Utility of diffusion tensor imaging studies linked to neuronavigation and other modalities in repeat hemispherotomy for intractable epilepsy

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OBJECTIVE Hemispherectomy for unilateral, medically refractory epilepsy is associated with excellent long-term seizure control. However, for patients with recurrent seizures following disconnection, workup and investigation can be challenging, and surgical options may be limited. Few studies have examined the role of repeat hemispherotomy in these patients. The authors hypothesized that residual fiber connections between the hemispheres could be the underlying cause of recurrent epilepsy in these patients. Diffusion tensor imaging (DTI) was used to test this hypothesis, and to target residual connections at reoperation using neuronavigation.

METHODS The authors identified 8 patients with recurrent seizures following hemispherectomy who underwent surgery between 1995 and 2012. Prolonged video electroencephalography recordings documented persistent seizures arising from the affected hemisphere. In all patients, DTI demonstrated residual white matter association fibers connecting the hemispheres. A repeat craniotomy and neuronavigation-guided targeted disconnection of these residual fibers was performed. Engel class was used to determine outcome after surgery at a minimum of 2 years of follow-up.

RESULTS Two patients underwent initial hemidecortication and 6 had periinsular hemispherotomy as their first procedures at a median age of 9.7 months. Initial pathologies included hemimegalencephaly (n = 4), multilobar cortical dysplasia (n = 3), and Rasmussen's encephalitis (n = 1). The mean duration of seizure freedom for the group after the initial procedure was 32.5 months (range 6–77 months). In all patients, DTI showed limited but definite residual connections between the 2 hemispheres, primarily across the rostrum/genu of the corpus callosum. The median age at reoperation was 6.8 years (range 1.3–14 years). The average time taken for reoperation was 3 hours (range 1.8–4.3 hours), with a mean blood loss of 150 ml (range 50–250 ml). One patient required a blood transfusion. Five patients are seizure free, and the remaining 3 patients are Engel Class II, with a minimum follow-up of 24 months for the group.

CONCLUSIONS Repeat hemispherotomy is an option for consideration in patients with recurrent intractable epilepsy following failed surgery for catastrophic epilepsy. In conjunction with other modalities to establish seizure onset zones, advanced MRI and DTI sequences may be of value in identifying patients with residual connectivity between the affected and unaffected hemispheres. Targeted disconnection of these residual areas of connectivity using neuronavigation may result in improved seizure outcomes, with minimal and acceptable morbidity.

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KEY WORDS epilepsy surgery; hemispherectomy; periinsular hemispherotomy; diffusion tensor imaging; neuronavigation

Hemispherectomy for children with unilateral, medically refractory epilepsy is associated with excellent long-term seizure control. Outcomes are dependent on achieving a complete disconnection between the affected, diffusely abnormal hemisphere and the normal hemisphere. For the 15%–30% of children with recurrent seizures following procedures such as periinsular hemispherotomy (PIH),12 regaining seizure control can be problematic—requiring the addition of new anticonvulsant medications, a trial with vagal nerve stimulation, or
conversion to anatomical hemispherectomy.\textsuperscript{15,30} Whereas the complications of hemispherectomy at the time of initial surgery, whether anatomical or functional, are well described,\textsuperscript{2,14,15,20} issues relating to repeat hemispherotomy are not as well described in the literature.

For children with persistent or recurrent seizures following hemispherectomy, it is imperative that the epilepsy surgery team determines if disconnection of the affected hemisphere has been successfully achieved. In addition to prolonged video electroencephalography (EEG) recordings to demonstrate the semiology of the recurrent/residual seizure pattern, MRI studies should be obtained to carefully demonstrate the completeness of the disconnection. Although this can sometimes be difficult given the complexities of the relevant association, commissural, and projection fiber systems—complexities that are caused by congenital or acquired anatomical deformity in the affected hemisphere—advances in MRI technology have made the determination of extent of disconnection easier to visualize, document, and correlate with the seizure semiology. In this regard, the development of MR fiber tractography in conjunction with diffusion tensor imaging (DTI) has the potential in theory to be used to study persistent white matter fiber tracts connecting the 2 hemispheres in postoperative cases of hemispherectomy for which seizure persistence or recurrence remains problematic.

A DTI investigation is based on the principle that the diffusivity of water molecules is restricted in highly organized tissues, such as white matter tracts, a process known as diffusion anisotropy.\textsuperscript{26} Diffusion anisotropy is influenced by intraaxonal organization, degree of myelination, density of fiber and neuroglial cell packing, and fiber diameter.\textsuperscript{21} Fractional anisotropy is a measure of anisotropy, and quantitative maps of fractional anisotropy can be generated, with higher signal representing greater degree of anisotropy.\textsuperscript{24} Color vector maps reflect both anisotropy and direction of the white matter, with intensity representing the anisotropy and color representing the direction of the white matter. A tensor can be modeled whereby the restricted diffusion is parallel to the direction of the fiber bundles.\textsuperscript{10} Fractional anisotropy and mean diffusivity are measures that are used to quantify tensor-like phenomena so that tractography and DTI maps can be created to estimate the position of relevant white matter fibers.

To date, there have been few studies that have examined the benefit of a comprehensive workup of the pediatric patient with failed hemispherectomy, including the use of DTI, to guide treatment aimed at disconnecting persistent connectivity fibers.\textsuperscript{3,28} Here we present our experience with a subset of patients who were identified as having persistent bands of white matter connectivity between the 2 hemispheres following hemispherectomy and who underwent targeted resection of these bands in attempts to improve their underlying intractable epilepsy. Our neurosurgical technique in these cases is described.

**Methods**

**Index Hemispheric Procedures Performed for Intractable Epilepsy**

Prior to 1997, the surgical approach to hemispherectomy at the Hospital for Sick Children, Toronto, was hemidecortication (HD). In 1997, a change in technique was adopted in favor of PIH, which has been used since that time for children with catastrophic, hemispheric epilepsy. Both techniques were described in detail recently.\textsuperscript{3,12} Briefly, HD is performed after a large unilateral craniotomy. The dura mater is typically opened widely, and the affected brain tissue is resected lobe by lobe from the cortex to the white matter, in stages. The Cavitron is used to resect the cortical tissue by aspirating within the white matter planes. In the end, only a small amount of cerebral tissue is left overlying the basal ganglia and deep gray matter structures such as the thalamus. The ventricle is not routinely exposed, and mesiotemporal structures are not resected in cases in which HD is used.\textsuperscript{9,17,26}

For PIH, the frontoparietal opercular cortex is resected down to the insular pial bank, creating the suprainsular window; the infrainsular window is created by resecting the temporal opercular cortex down to the pia overlaying the insula.\textsuperscript{31,32} Typically, an anterolateral temporal lobectomy including mesial structures is performed in most cases. The corona radiata is then transected following the opening of the lateral ventricular system. A complete callosotomy is performed from within the lateral ventricle, using the pericallosal vessels anteriorly and the free edge of the falx and tentorium posteriorly as delimiting structures. A frontal disconnection is then performed by following the pia along the medial sphenoid wing of the anterior cranial fossa floor to the interhemispheric fissure, and by joining it to the frontal ventricular horn incision. Finally, the insular cortex is resected either en bloc or piecemeal, depending on the position of the penetrating insular cortical arterial candelabra.

**Patient Workup and Investigation Following Failed HD or PIH**

This series includes pediatric patients with recurrent seizures following an initial hemispherectomy that was performed between 1995 and 2012. With the recurrence of seizures, all patients were extensively re-investigated with routine EEG, prolonged video EEG recordings in the epilepsy monitoring unit, and neuroimaging (MRI scan—either 1.5 or 3 T). MRI studies included high-resolution volumetric T1-weighted imaging as well as axial and coronal T2-weighted imaging and proton density, FLAIR, and DTI sequences. Color vector maps and fractional anisotropy maps were generated from the DTI.

Magnetoecephalography (MEG) was performed in select cases as previously described.\textsuperscript{29} The results of all of these investigations were discussed at a multidisciplinary pediatric epilepsy surgery conference.

**Repeat Neurosurgical Procedure for Recurrent Epilepsy**

In preparation for repeat craniotomy, the volumetric T1-weighted and DTI sequences of all patients were imported into the BrainLab workstation for intraoperative navigation. Identification of the areas of suspected persistent connectivity were outlined and color coded by the neuroradiologist (E.W.). The patient’s head was rigidly fixed with a Sugita headrest for frameless stereotactic neu-
ronavigation. The previous skin incision was used, and a repeat craniotomy was performed, centered on the region of persistent connectivity. The dura was opened, the microscope was brought in, and the neuronavigation probe was used to identify the region of interest and the residual points of connectivity on DTI. A targeted disconnection was then performed using microneurosurgical technique. A postoperative external ventricular drain was then placed at the neurosurgeon’s discretion.

Seizure Outcome
Seizure outcome was graded using the Engel outcome scale for epilepsy surgery.8

Illustrative Cases
Case 1
The patient presented with catastrophic epilepsy at age 3 months and was diagnosed with left hemimegalencephaly on MRI (Table 1). A left HD procedure was performed at 8 months of age. Seizures were not improved, and the child required 2 additional procedures resecting residual cortex, leaving the basal ganglia behind (Fig. 1). The child also required insertion of a ventriculoperitoneal (VP) shunt. Following these procedures, seizures were still not improved, the child’s seizure outcome remained Engel Class IV, and he was receiving 4 antiseizure medications. His primary seizure type comprised complex partial seizures with secondary generalization. At age 15 years, 3-T MRI and DTI were performed and demonstrated persistent connectivity between a small remnant of basal frontal cortex and the corpus callosum (Fig. 1). A small frontal craniotomy was performed, and the area of suspected basal frontal connectivity was sectioned at the level of the corpus callosum using DTI-guided neuronavigation. The postoperative recovery was uneventful. Following this, the patient attained Engel Class II seizure outcome and was receiving 2 anticonvulsant medications at the 2-year follow-up.

Case 4
At the age of 6 years, the patient presented with sudden-onset intractable epilepsy. Workup and investigation, including MRI, suggested right Rasmussen’s encephalitis. A temporal lobe biopsy was performed, the results of which supported the diagnosis. A right PIH was then performed, and the patient became seizure free for 7 years and was successfully weaned from his medications. At the age of 13 years, his seizures recurred and comprised complex partial seizures with suspected right frontal lobe onset. DTI sequences suggested a small region of persistent connectivity between the basal frontal lobe and the corpus callosum (Fig. 2). A second surgery was performed via a small frontal craniotomy, followed by resection of this band of connectivity, for which neuronavigation and microneurosurgical technique were used. No postoperative complications were noted. Following surgery, the child once again became seizure free, was weaned from his medications, and was Engel Class I at 2 years postoperatively.

Results
Patient Demographic Data, Neuropathological Findings, and Initial Seizure Outcome
Between 1995 and 2012, 88 children underwent hemispherectomy for catastrophic epilepsy at the Hospital for Sick Children. Between 1995 and 1997, 8 patients underwent HD; whereas 80 patients underwent PIH between 1997 and 2012. In the time period of this study, 8 of 88 patients (9.1%) were identified who experienced recurrent seizures after hemispherectomy, with suspected fiber tract connectivities between the 2 hemispheres. Two patients had prior HD procedures, whereas 6 had prior PIH. There were 3 males and 5 females. Initial seizure onset occurred at a median of 2.6 months (range newborn to 6 years). Initial PIH or HD was performed at a median age of 9.7 months (range 2–72 months). The neuropathological diagnoses included hemimegalencephaly (n = 4), hemispheric corti-
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Initial Procedure</th>
<th>Initial Pathology</th>
<th>Time to Sz Recur</th>
<th>Prolonged VEEG at Recur</th>
<th>Findings on MRI/DTI at Recur</th>
<th>Time From Recur to Reop</th>
<th>Surgical Procedure Performed w/ Neuronavigation</th>
<th>Engel Class Outcome At 2 Yrs</th>
<th>At Last Follow-Up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lt HD</td>
<td>Hemimegalencephaly</td>
<td>6 mos</td>
<td>Lt frontotemporal Szs</td>
<td>Remnant of rostrum/genu of corpus callosum</td>
<td>120 mos</td>
<td>Lt frontotemporal craniotomy, division of rostrum</td>
<td>II</td>
<td>II (5 yrs)</td>
</tr>
<tr>
<td>2</td>
<td>Rt HD</td>
<td>Hemispheric cortical dysplasia</td>
<td>36 mos</td>
<td>Rt temporal Szs</td>
<td>Remnant of rostrum of corpus callosum &amp; ant commissure, remnant of rt ant temporal lobe</td>
<td>36 mos</td>
<td>Rt frontotemporal craniotomy, division of rostrum, removal of ant temporal lobe, section of ant commissure</td>
<td>I</td>
<td>I (3 yrs)</td>
</tr>
<tr>
<td>3</td>
<td>Lt PIH</td>
<td>Hemimegalencephaly</td>
<td>48 mos</td>
<td>Lt frontal Szs</td>
<td>Remnant of rostrum of corpus callosum</td>
<td>60 mos</td>
<td>Lt frontotemporal craniotomy, division of rostrum</td>
<td>II</td>
<td>II (3 yrs)</td>
</tr>
<tr>
<td>4</td>
<td>Rt PIH</td>
<td>Rasmussen's encephalitis</td>
<td>77 mos</td>
<td>Rt frontal-onset Szs</td>
<td>Remnant of rostrum/genu of corpus callosum</td>
<td>15 mos</td>
<td>Rt frontotemporal craniotomy, division of rostrum</td>
<td>I</td>
<td>III (4 yrs)†</td>
</tr>
<tr>
<td>5</td>
<td>Lt PIH</td>
<td>Hemispheric cortical dysplasia</td>
<td>13 mos</td>
<td>Periodic rt arm spasms</td>
<td>Residual lt insular cortex, amygdala, &amp; temporal pole</td>
<td>6 mos</td>
<td>Lt temporal craniotomy, removal of lt insular cortex, amygdala, &amp; temporal pole</td>
<td>I</td>
<td>I (2.5 yrs)</td>
</tr>
<tr>
<td>6</td>
<td>Lt PIH</td>
<td>Hemimegalencephaly</td>
<td>20 mos</td>
<td>Lt frontotemporal Szs</td>
<td>Residual lt mesial &amp; ant temporal lobe</td>
<td>9 mos</td>
<td>Lt temporal craniotomy, lt temporal lobectomy</td>
<td>I</td>
<td>I (3 yrs)</td>
</tr>
<tr>
<td>7</td>
<td>Rt PIH</td>
<td>Hemispheric cortical dysplasia</td>
<td>24 mos</td>
<td>Rt frontal Szs</td>
<td>Remnant of rostrum of corpus callosum &amp; mesial frontal lobe</td>
<td>12 mos</td>
<td>Rt frontal craniotomy, division of rostrum; completion of frontal disconnection</td>
<td>I</td>
<td>I (2.8 yrs)</td>
</tr>
<tr>
<td>8</td>
<td>Rt PIH</td>
<td>Hemimegalencephaly</td>
<td>36 mos</td>
<td>Rt frontotemporal Szs</td>
<td>Remnant of rostrum of corpus callosum &amp; residual ant temporal lobe</td>
<td>14 mos</td>
<td>Rt frontotemporal craniotomy, division of rostrum, temporal lobectomy</td>
<td>II</td>
<td>II (3 yrs)</td>
</tr>
</tbody>
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Ant = anterior; Recur = recurrence; Sz = seizure; VEEG = video EEG.

* Data are given as Engel class, with total time since repeat hemispherotomy in parentheses.
† Recent relapse with seizures. Workup and investigation now demonstrate relapse in previously unaffected, normal hemisphere.
Persistent spike-wave disturbances from the surgically treated hemisphere coincided with clinical seizure onset. Careful attention was paid to the semiology of the seizure events to ensure that those captured were stereotypical and concordant with the other data from the workup. In all 8 patients, DTI demonstrated residual connectivity from the surgically treated hemisphere to the contralateral side across the corpus callosum from residual basal frontal lobe; across the anterior commissure from retained temporal lobe elements; or from demonstrated residual insular cortex (Table 1). An additional demonstration of the potential value of DTI in our case series is shown in Fig. 3, which highlights areas of persistent connectivity not so clearly seen on T1-weighted MRI in another patient. MEG was performed in 4 patients; in 3 of them, spike clusters were found over the affected hemisphere in a distribution consistent with the suspected seizure onset zone.

**Operative Findings, Postoperative Course, and Seizure Outcome**

The median time from seizure recurrence to reoperation for the group was 14.5 months (range 6–120 months; mean 34 months). The median age at second surgery was 6.8 years (range 1.3–14 years). Average operative duration was 3 hours (range 1.8–4.3 hours) with a mean blood loss of 150 ml (range 50–250 ml). One patient required a blood transfusion. The average hospital stay was 7 days (range 6–11 days). All patients were discharged home without further physiotherapy or rehabilitation requirements. There were no cases of infection or aseptic meningitis. There were no new cases of hydrocephalus or shunt failure. There were no new neurological deficits in any of the cases. One patient experienced an asymptomatic hemorrhagic conversion of a prior occipital lobe infarct. Five children were seizure free, and 3 had an Engel Class II outcome with a minimum follow-up of 24 months.

**Discussion**

In this series, we have shown that children with recurrent epilepsy after hemispheric disconnection procedures may benefit from reoperation in which surgery is targeted at demonstrated areas of persistent connectivities between the 2 hemispheres. Using a combination of repeat video EEG monitoring, MRI, MEG, DTI, and intraoperative neuronavigation, we have been successful at identifying residual white matter tract connectivities causing recurrent epilepsy. Transection of these residual white matter tracts has been a successful means by which these children can be rendered either seizure free or in a better seizure outcome state.

Children with catastrophic epilepsy typically fit into one of the main categories of disease processes that affect the brain and for which hemispherectomy is recommended. In this group of patients, one can expect a 70%–85% chance of seizure freedom following hemispherectomy. The technique of hemispherectomy has evolved over the past 30 years to include approaches that primarily disconnect the affected hemisphere from the contralateral side, and that have become more minimally invasive, requiring less cerebral tissue to be removed. All...
though these advancements have led to expedited patient recovery and diminished length of stay in hospital, just as with anatomical hemispherectomy, there are instances of seizure recurrences or failures that arise after PIH or other functional disconnection procedures. Such patients with recurrent epilepsy after PIH can be problematic to investigate, and it can be difficult to make determinations regarding further treatments.

Recently, Vadera et al. described their experience with 36 patients who underwent reoperative hemispherotomy for diffuse unilateral hemispheric disease. These authors reported that prior to anatomical hemispherectomy, preoperative MRI studies showed that 44% of disconnections appeared to be complete, 44% appeared incomplete, and 11% were unknown. These investigators also showed that review of the MRI findings after PIH revealed the basal frontal and insular regions as the most likely sources of recurrent seizures, similar to the findings in our study. In their study, the majority of patients experienced improved seizure outcome on conversion of a PIH to an anatomical hemispherectomy. Finally, Vadera et al. determined that generalized ictal EEG activity before the repeat hemispherotomy and histopathological findings of cortical dysplasia correlated with a poorer prognosis in their patient population.

Both HD and PIH allow for good to excellent seizure control while minimizing acute and long-term sequelae when compared with anatomical hemispherectomy. We have previously shown in our series of patients with hemispherectomy that PIH was superior to HD for control of catastrophic epilepsy. We have also characterized the relevance of spike clusters in children undergoing hemispherectomy. In this study, we have shown that MEG performed at recurrence of seizures posthemispherectomy can be used as additive information together with prolonged video EEG recordings and MRI/DTI. The potential true value of EEG and MEG is in determining the unilateral nature of the epileptic disturbances to the affected hemisphere and excluding patients who may possibly exhibit bihemispheric disturbances.

Use of DTI can supplement detailed anatomical imaging to identify residual white matter connections that could be responsible for seizure propagation. That being stated, tractography has been of considerable value for neurosurgeons embarking on intraaxial brain tumor surgeries. In this situation, DTI allows for the visualization of the relationship between a neoplasm and the surrounding white matter tracts for both preoperative planning and intraoperative resection when combined with neuronavigation. However, the use of DTI in epilepsy surgery has been limited to a few descriptive studies. Toda et al. described a case of a 5-year-old boy who underwent PIH for hemispheric epilepsy resulting from diffuse hemispheric cortical dysplasia. Three months after hemispherotomy, the child developed recurrent seizures. MRI and DTI were performed during follow-up, and these studies demonstrated residual crossing fibers at the genu of the corpus callosum. On further resection of the genu in this case, the patient became seizure free once again, although the length of follow-up was not provided. In the current study, DTI was of value in identifying persistent white matter tracts, including the rostrum/genu of the corpus callosum and the anterior commissure, which connects bilateral temporal lobes. Resection of the remnant temporal lobe would effectively remove the connection with the normal temporal lobe. It should be stated here that thin-slice T1-weighted images, particularly in the coronal plane, are also of considerable value in evaluating the persistence of connectivities between the 2 hemispheres.

Neuronavigation is used routinely in neurosurgery in the developed world. We have been using neuronavigation for complex pediatric neurosurgical procedures since...
In the present series, neuronavigation was extremely helpful and reliable in delineating the residual white matter tracts of connectivity across the corpus callosum and anterior commissure. The neuroanatomy of the lateral ventricle, the anterior cerebral and pericallosal arteries, and the interhemispheric fissure may be somewhat distorted at the time of repeat hemispherotomy—hence the value of a tracking system such as neuronavigation.

Having studied our failed cases in detail, we conclude that the main reason for failure was incomplete resection of the rostrum/genu of the corpus callosum, especially at its most inferior and anterior segment. Although the pericallosal arteries serve as valuable and important landmarks for marking the midline approach to sectioning the corpus callosum during PIH, these arteries deviate from the corpus callosum the more proximally the neurosurgeon follows them toward the A2 and A1 segments of the anterior cerebral artery. The second most common reason for failure was the presence of residual temporal lobe with a persistent anterior commissure. Based on our experience, it is therefore critical during initial PIH surgery that the corpus callosum at its rostrum be sectioned carefully and completely to ensure that disconnection has been achieved.

Interestingly, many of our patients were seizure free for several years prior to the recurrence of their seizures. This may reflect the fact that disrupting the vast majority of connections between the 2 hemispheres renders a patient in a seizure-free state after incomplete hemispherotomy. Over time, and with the continued presence of neuropsychologically and electrically abnormal cerebral tissue and networks in the retained hemisphere, alternate epileptogenic pathways may develop, leading to the onset of recurrent epilepsy. The median time from seizure recurrence to reoperation for the group was 14.5 months. This relatively long time to repeat disconnection reflects the time taken to adjust anticonvulsant medications in some cases, and the time to repeat the epilepsy surgery workup, including video EEG and MEG, among other studies.

Despite the repeat hemispherotomies we performed in this series, there were 3 patients (37.5%) who continued to have seizures even though we were satisfied with our determination that the hemispheric disconnection was now complete. As in the case series by Vadera et al. in which there was a 36% failure rate of anatomical hemispherectomy after PIH, we have concluded that these cases may well represent true bihemispheric epilepsy.

In the future, it would be interesting and important to conduct a prospective study in which DTI is used postoperatively in all patients following PIH to assess the extent of disconnection and to determine how many patients will demonstrate seizure recurrence with or without identifiable tracts of residual connectivity between the hemispheres.

**Conclusions**

The options available to children who have undergone PIH or other functional hemispheric procedures for catastrophic epilepsy are somewhat limited. Here, we provide our experience with a series of patients in whom recurrent epilepsy was traced back to persistent white matter tracts that were not identified or appreciated at the time of original surgery. We suggest that it is an option to consider repeat hemispherotomy in these patients, provided that the seizure semiology and the electrophysiological and neuroimaging studies are concordant. Conversion to an anatomical hemispherectomy may not always be necessary in this population of patients. We have shown that repeat surgery to ensure that a complete disconnection has been accomplished carries an acceptable risk and is straightforward and beneficial in the majority of our patients. In these children, our efforts provided them with a second opportunity to achieve long-term good seizure control.

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**References**


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