The role of hemispherectomy in the treatment of holohemispheric hemimegalencephaly

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The role of hemispherectomy in treating holohemispheric hemimegalencephaly, a unilateral brain malformation, is still not well defined. The authors describe the cases of five infants presenting with intractable seizures, progressive neurological deficits, and severe developmental delay. Electroencephalography (EEG) showed generalized polyspikes from the megalencephalic hemisphere and progressive slowing on the opposite side in all children; contralateral seizure spikes occurred in three children. Three of the five children underwent hemispherectomy for intractable seizures before 2 years of age, after which the seizures subsided completely in two children and improved remarkably in the third. Preoperative Wada testing proved useful in evaluating pharmacologically the effect of hemispherectomy on contralateral polyspikes. Postoperative EEG revealed the absence of polyspikes in the operated hemisphere and decreased slowing on the contralateral side. Psychomotor development in the surgically treated infants exceeded that of the children not undergoing hemispherectomy. Of the two children treated medically, one died at 4 years of age in status epilepticus and the other (now 5 years old) has frequent seizures and severe developmental delay.

Based on these results, hemispherectomy appears to be a useful procedure for controlling seizures and improving psychomotor development in children with hemimegalencephaly involving the entire hemisphere. Surgery in infancy can prevent or minimize seizure foci and encephalopathic changes that may develop in the contralateral hemisphere. Staging the procedure and exercising meticulous hemostasis make surgery relatively safe in infants who otherwise may have significant blood loss associated with increased blood flow to the megalencephalic hemisphere.

Key Words: hemimegalencephaly • hemispherectomy • seizure • Wada test • infant

Hemimegalencephaly, a rare developmental disorder of neuronal migration during the 3rd month of gestation, is a unilateral brain malformation. This disorder ranges from mild forms affecting part of the cerebral lobe to more severe forms involving the entire hemisphere (holohemispheric). Holohemispheric hemimegalencephaly is characterized clinically by intractable seizures, severe psychomotor delay, marked encephalopathy, and death in infancy. The treatment of children with this serious condition has had disappointing results. Callosotomy and ventricular shunting have been unsuccessful in controlling seizures and encephalopathic changes. Although hemispherectomy has recently been advocated to treat holohemispheric hemimegalencephaly, the experience is limited to a few case reports.

To better define the role of hemispherectomy in treating holohemispheric hemimegalencephaly, we present the cases of five infants diagnosed as having this condition. Their clinical course with or without surgical intervention is described and the results following the insertion of ventricular shunts, partial hemispherectomy, and complete hemispherectomy are reviewed.

Clinical Material and Methods

Clinical Diagnosis

The charts of five children with hemimegalencephaly involving the entire hemisphere were reviewed; these patients were diagnosed and treated at the Children's Hospital Medical Center in Cincinnati, Ohio, between 1984 and 1991. Diagnosis was made by computerized tomography or magnetic resonance (MR) imaging, which showed in each child the radiological changes typical of holohemispheric hemimegalencephaly. These findings included hypertrophy of the entire cerebral hemisphere with displacement of midline structures to the opposite side, ipsilateral ven-
triculomegaly, abnormal gyri with shallow sulci and thickened cortex, subcortical calcifications and heterotopia, and increased white matter signal on T2-weighted MR images (Fig. 1). In four children, the diagnosis was confirmed by histological examination of cerebral tissue obtained either during surgery or at autopsy. The histological criteria20 for diagnosis of hemimegalencephaly include various combinations of the following: a firm and hypertrophied hemisphere with a dilated ventricle, wide cortical gyri with shallow sulci and broad cerebral convolution, thickened cortex and white matter, disorganized cortical cytoarchitecture and loss of all cortical lamination, the presence of giant neurons scattered within the cortex, diffuse neuronal hypertrophy and hyperplasia, white matter gliosis with absence of astroglial proliferation, and subcortical heterotopia. All of these findings were unilateral.

Clinical Presentation

Table 1 summarizes the clinical presentations of the five infants (three boys and two girls). Hemimegalencephaly was identified in the right hemisphere in three infants (Cases 1, 3, and 4) and in the left hemisphere in two (Cases 2 and 5). Each child presented with intractable seizures, developmental delays, progressive contralateral and ipsilateral neurological deficits, and a decline in social behavior. Seizures started within 2 weeks following birth in four children and at 4 months of age in one child (Case 4) (Table 2). Each child had generalized tonic-clonic seizures, starting on the side opposite to the hemimegalencephaly; two children (Cases 3 and 5) had myoclonic jerks. Electroencephalography (EEG) in all children showed generalized polyspikes over the megalencephalic hemisphere and progressive slowing on the opposite side. Three children (Cases 1, 2, and 5) had seizure spikes in the normal hemisphere. In two children (Cases 1 and 2), these spikes were partly autonomous as recorded by EEG.

Treatment

Table 3 summarizes treatment of these five cases. Each child received maximum medical treatment for seizures, including phenytoin, phenobarbital, carbamazepine, and valproic acid. In four children (Cases 1 to 4), ventriculoperitoneal shunts were placed. In three children, hemispherectomy was performed in two stages; at 6 and 9 months in Case 1, at 17 and 21 months in Case 2, and at 6 and 19 months in Case 3. Hemispherectomy included the entire megalencephalic hemisphere.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Abnormal Hemisphere</th>
<th>Seizures</th>
<th>Neurological Deficits</th>
<th>Developmental Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>rt</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>lt</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>3</td>
<td>F</td>
<td>rt</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>rt</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>lt</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Seizures = > 10 seizures per day despite multiple antiepileptic agents; neurological deficits = progressive contralateral and ipsilateral neurological deficits; + = feature present.

**TABLE 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Seizure Onset</th>
<th>Seizure Pattern</th>
<th>Results of Electroencephalography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 days</td>
<td>F, GTC</td>
<td>diffuse spikes, slowing, spikes†</td>
</tr>
<tr>
<td>2</td>
<td>1 day</td>
<td>F, GTC</td>
<td>diffuse spikes, slowing, spikes†</td>
</tr>
<tr>
<td>3</td>
<td>12 days</td>
<td>F, GTC, M</td>
<td>diffuse spikes, slowing</td>
</tr>
<tr>
<td>4</td>
<td>4 mos</td>
<td>F, GTC</td>
<td>diffuse spikes, slowing</td>
</tr>
<tr>
<td>5</td>
<td>2 days</td>
<td>F, GTC, M</td>
<td>diffuse spikes, slowing, spikes</td>
</tr>
</tbody>
</table>

*Abbreviations: F = focal; GTC = generalized tonic-clonic; M = myoclonic.
† Independent spikes.
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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Medical Treatment</th>
<th>Ventriculoperitoneal Shunt</th>
<th>Partial Hemispherectomy (age at surgery)</th>
<th>Complete Hemispherectomy (age at surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+ (6 mos)</td>
<td>+ (9 mos)</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+ (17 mos)</td>
<td>+ (21 mos)</td>
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<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>+ (6 mos)</td>
<td>+ (19 mos)</td>
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<tr>
<td>4</td>
<td>+</td>
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<tr>
<td>5</td>
<td>+</td>
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</tr>
</tbody>
</table>

* Abbreviations: + = treatment given; — = treatment not given.
† Treatment consisted of multiple antiepileptic agents.
‡ Hemispherectomy involved the whole hemisphere in Cases 1 and 2 and spared the occipital lobe in Case 3.

hemisphere in two children (Cases 1 and 2); the occipital lobe was excluded in one child (Case 3) based on preoperative and intraoperative EEG, which showed no seizure spikes in the occipital lobe. Intraoperative electroencephalographic recordings were obtained in two children (Cases 1 and 3). Two infants with seizure spikes in the normal hemisphere (Cases 1 and 2) underwent Wada testing before hemispherectomy. In this test, normobarital was injected into the internal carotid artery that supplied the megalencephalic hemisphere in an attempt to silence its epileptogenic activity and to determine the effect of the drug on contralateral seizure spikes. Hemispherectomy was performed in two infants (Cases 1 and 2) with a fiberoptic laser and ultrasonic aspirator (Fig. 2). At their family's request, two children (Cases 4 and 5) did not undergo hemispherectomy.

Follow-Up Examination

The children were followed for 27 to 72 months (mean 48 months) and underwent frequent neurological examinations during treatment. Psychomotor and developmental skills were periodically assessed by Denver charts. All children had multiple electroencephalographic recordings before and after medical or surgical treatment.

Results

Effect of Ventricular Shunting on Outcome

In the four children who underwent ventricular shunting (Cases 1 to 4), symptoms of increased intracranial pressure (including vomiting and irritability) improved slightly. There were no changes in pattern or frequency of the seizures, focal neurological deficits, psychomotor development, or social behavior.

Outcome in Children Not Undergoing Hemispherectomy

Both children who did not undergo hemispherectomy (Cases 4 and 5) had poor outcomes. Intractable seizures persisted despite intensive medical treatment.

One child (Case 5) had severe psychomotor retardation, estimated as a developmental age of 14 months at the chronological age of 52 months. He subsequently died in status epilepticus at the age of 55 months. The other child (Case 4), still alive at 68 months of age, has frequent seizures, poor social insight, and severe psychomotor retardation, estimated as 8 months of age developmentally. Both children had progressive neurological deficits; EEG showed progressive encephalopathic changes in both hemispheres.

Outcome in Children Undergoing Hemispherectomy

All three children who underwent hemispherectomy improved and are alive at the ages of 6 years (Case 1), 2½ years (Case 2), and 4½ years (Case 3). Their outcomes are summarized as follows.

Seizure Control. Seizures either improved remarkably or subsided totally in all three children. In Case 1, seizures improved following partial hemispherectomy and subsided completely immediately following complete hemispherectomy. This child is still seizure-free and off all medications 6 years after hemispherectomy. In Case 2, seizures improved after partial hemispherectomy and generalized seizures subsided immediately after complete hemispherectomy. Although this child continues to have occasional focal seizures involving the side ipsilateral to the hemimegalencephaly (generated from contralateral-independent seizure spikes), medications have controlled these seizures for 2½ years after surgery. In Case 3, seizures improved following resection of the temporal and parietal lobes and parts of the frontal lobe; seizures subsided completely following resection of the remaining frontal lobe, which showed increased epileptogenic activity 8 months following the first surgery. This child remains seizure-free without medication 3 years after her last surgery.

Postoperative Electroencephalographic Results. All three children who underwent hemispherectomy had total resolution of polyspikes in the megalencephalic hemisphere and marked reduction of slowing in the
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contralateral hemisphere after surgery. In Case 1, although initial seizure activity was reduced in the megalencephalic hemisphere after partial hemispherectomy, seizure spikes in the remaining occipital lobe had increased 8 months later as seizure activity spread to the opposite side. Following complete hemispherectomy, seizure activity in both hemispheres subsided, including seizure spikes in the normal hemisphere, which were judged by preoperative EEG to be partly independent. In this child, Wada testing proved to be more accurate than EEG in evaluating preoperatively the effect of hemispherectomy on contralateral seizure spikes. These seizure spikes subsided totally following electrical silencing of electroencephalographic activity in the megalencephalic hemisphere after amobarbital injection. In Case 2, contralateral seizure spikes persisted after hemispherectomy; these spikes were partly independent on preoperative EEG. Preoperative injection of amobarbital failed to silence either the electroencephalographic activity in the megalencephalic hemisphere or the contralateral seizure spikes. In Case 3, the child did not have contralateral seizure spikes. Based on preoperative and intraoperative EEG, the frontal pole was not excised during the first hemispherectomy. However, seizure activity in the remaining frontal pole increased 8 months following hemispherectomy, necessitating excision. In the remaining occipital lobe, seizure spikes did not occur either preoperatively or 2 years postoperatively.

Neurological Deficits. Although quantitative measurement of motor skill improvement is difficult in this age group, serial neurological examinations were used to assess such improvement. All three children were followed and assessed by the operating neurosurgeon, physical therapist, and rehabilitation team. None of the children developed hemiparesis attributed to the operation. Ipsilateral motor weakness, which was present preoperatively, resolved completely within 1 to 2 weeks after hemispherectomy. Functions that resumed within a month included control of the head position, raising the head more than 45° from the prone position, the ability to roll from supine to prone, use of rotational rolling, and sitting without support. The improvement of contralateral hemiplegia was less remarkable: slower (up to 6 months) and without fine motor movements. Such improvement included the ability to kick a leg when prone or supine, raising a hand to midline, reaching a hand against gravity, and raising a leg off the mattress. None of the children could cross their arms beyond midline or substantially move their fingers.

Psychomotor and Social Development. All three children undergoing hemispherectomy showed remarkable improvement in their psychomotor and social development within 1 week. They became less irritable as well as more sociable, alert, and involved with their surroundings. When evaluated with the Denver Developmental Screening Test, these children showed significant improvement in the ratio of estimated developmental age to chronological age after hemispherectomy. On follow-up examination, the estimated developmental age:chronological age ratios of children who underwent hemispherectomy were higher than those who did not (Fig. 3).

Cerebrospinal Fluid Shunting After Hemispherectomy. Two of three children who underwent hemispherectomy developed symptomatic hydrocephalus
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Fig. 4. Case 1. Computerized tomography scans in an infant who underwent hemispherectomy for holohemispheric hemimegaloencephaly. Left: Preoperative image. Center: Cisternographic scan. Right: Postoperative scan.

(symptoms included headache, irritability, vomiting, and drowsiness) and required further treatment. One child underwent modification of a right ventriculoperitoneal shunt for proximal obstruction 2 months after undergoing a right hemispherectomy (Fig. 4) and the other child underwent insertion of a ventriculoperitoneal shunt for left ventricular enlargement 6 months after undergoing a right hemispherectomy. In both cases, symptoms resolved after shunting.

Discussion

Review of the Literature

Prior to 1980, 10 children with documented holohemispheric hemimegaloencephaly were described in the literature. Hemispherectomy was performed on two of these children, at 4 1/2 and at 13 months of age. One child died 24 hours following surgery and the other remained in a vegetative state for 2 1/2 years before he died. In 1985, King, et al., were the first to report a favorable outcome following hemispherectomy in a 5-month-old infant with holohemispheric hemimegaloencephaly, who ceased having seizures and showed early improvement of psychomotor development after surgery.

Since then, several reports discussing the clinical, radiological, and pathological aspects of children with holohemispheric hemimegaloencephaly have included hemispherectomy as a form of treatment for a few children; however, the results of surgery were not reported. In 1989, Hoffman and Raffel reported on two infants with holohemispheric hemimegaloencephaly who underwent hemispherectomy in infancy; one infant died from bleeding while the other survived without seizures but with severe psychomotor retardation. In the same year, Vigevano, et al., reported favorable results in two children with holohemispheric hemimegaloencephaly who underwent hemispherectomy at 2 1/2 and at 3 years of age. Both children suddenly and completely recovered from seizures and showed improved psychomotor development. Although the authors concluded that hemispherectomy was a successful procedure for intractable seizures in children with holohemispheric hemimegaloencephaly, they discouraged such treatment because of the high associated morbidity and mortality rates following surgery in this age group. They also advocated continuous and prolonged preoperative electroencephalographic monitoring to exclude the presence of seizure foci in the normal hemisphere. Although some authors believed that spikes in a normal hemisphere do not contraindicate hemispherectomy on the opposite side, Vigevano, et al., stated that seizure foci in the normal hemisphere could compromise the success of hemispherectomy in controlling seizures and might represent a relative contraindication to hemispherectomy.

Effect of Hemispherectomy on Psychomotor Development

Because continued frequent seizures can functionally compromise normal brain, one may assume that a better outcome is achieved with prompt seizure control by the early reversal of encephalopathic changes that occur in the contralateral hemisphere. Based on our experience, we do not agree that a young age is necessarily a limiting factor for patients undergoing hemispherectomy. Although Walters, et al., suggested that blood flow to the megaloencephalic hemisphere may be increased, we believe that meticulous hemostasis can minimize blood loss in infants undergoing hemispherectomy for holohemispheric hemimegaloencephaly, thus making the procedure relatively safe. If, however, the surgeon encounters significant blood loss during surgery, the procedure may be staged. We have found the use of a fiberoptic hemostatic laser to be particularly helpful in minimizing such blood loss during hemispherectomy. In our series all patients were op-
erated on in one or two stages before 2 years of age; all had significant improvement in neurological deficits and psychomotor development.

**Effect of Hemispherectomy on Seizure Control**

In our series, ventriculoperitoneal shunting was unsuccessful in controlling seizures or improving psychomotor development and thus cannot be recommended as the sole form of surgical treatment in children with holohemispheric hemimegalencephaly; others have had similar experiences. On the other hand, the effect of hemispherectomy on seizure control was dramatic. This was true irrespective of the presence of "independent" seizure foci in the normal hemisphere, which may or may not resolve following hemispherectomy. Based on our results, we do not recommend continuous preoperative electroencephalographic monitoring. In this regard, preoperative Wada testing may prove more useful than EEG in assessing independent seizure foci in the normal hemisphere and the effect of hemispherectomy on these spikes. Even if true independent seizure spikes in the normal hemisphere are found, hemispherectomy should be recommended because seizure control may still improve, as in our Case 3.

**Conclusions**

Based on these results, we offer the following conclusions.

1. Seizures lessen after partial hemispherectomy and may subside immediately after complete hemispherectomy in children with holohemispheric hemimegalencephaly.

2. Wada testing may prove useful in assessing preoperatively the effect of hemispherectomy on contralateral seizure spikes.

3. Contralateral independent seizure spikes should not contraindicate hemispherectomy.

4. Following hemispherectomy, improvement was noted in both ipsilateral and contralateral neurological motor deficits and in social and psychomotor development.

5. Theoretically, earlier surgery may arrest contralateral encephalopathic changes caused by chronic seizures.

6. Intraoperative blood loss during hemispherectomy in infants can be reduced by meticulous hemostasis. If blood loss during the procedure is still significant, the surgeon may need to stage the procedure.

**Acknowledgments**

The authors thank John M. Tew, Jr., M.D., for technical review and Mary Kemper for editorial assistance.

**References**


Manuscript received June 26, 1992.
Accepted in final form October 13, 1993.
This paper was presented at the meeting of the Pediatric Section of the American Association of Neurological Surgeons held in Boston, December 3–6, 1991.

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