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Long-Term Outcomes of Hemispheric Disconnection in Pediatric Patients with Intractable Epilepsy

Yun-Jeong Lee,[a*] Eun-Hee Kim,[a*] Mi-Sun Yum,[a] Jung Kyo Lee,[b] Seokho Hong,[b] Tae-Sung Ko[a]

[a]Division of Pediatric Neurology, Department of Pediatrics, Asan Medical Center Children's Hospital, Seoul, Korea
[b]Department of Neurosurgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background and Purpose Hemispherectomy reportedly produces remarkable results in terms of seizure outcome and quality of life for medically intractable hemispheric epilepsy in children. We reviewed the neuroradiologic findings, pathologic findings, epilepsy characteristics, and clinical long-term outcomes in pediatric patients following a hemispheric disconnection.

Methods We retrospectively studied 12 children (8 males) who underwent a hemispherectomy at Asan Medical Center between 1997 and 2005. Clinical, EEG, neuroradiological, and surgical data were collected. Long-term outcomes for seizure, motor functions, and cognitive functions were evaluated at a mean follow-up of 12.7 years (range, 7.6−16.2 years) after surgery.

Results The mean age at epilepsy onset was 3.0 years (range, 0−7.6 years). The following epilepsy syndromes were identified in our cohort: focal symptomatic epilepsy (*n*=8), West syndrome (*n*=3), and Rasmussen's syndrome (*n*=1). Postoperative histopathology of our study patients revealed malformation of cortical development (*n*=7), encephalomalacia as a sequela of infarction or trauma (*n*=3), Sturge-Weber syndrome (*n*=1), and Rasmussen's encephalitis (*n*=1). The mean age at surgery was 6.5 years (range, 0.8−12.3 years). Anatomical or functional hemispherectomy was performed in 8 patients, and hemispherotomy was performed in 4 patients. Eight of our 12 children (66.7%) were seizure-free, but 3 patients with perioperative complications showed persistent seizure. Although all patients had preoperative hemiparesis and developmental delay, none had additional motor or cognitive deficits after surgery, and most achieved independent walking and improvement in daily activities.

Conclusions The long-term clinical outcomes of hemispherectomy in children with intractable hemispheric epilepsy are good when careful patient selection and skilled surgical approaches are applied.
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Key Words seizure, hemispherectomy, hemispherotomy, psychomotor outcomes.

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Correspondence
Tae-Sung Ko, MD
Department of Pediatrics,
Asan Medical Center,
University of Ulsan
College of Medicine, 88
Olympic-ro 43-gil, Songpa-gu,
Seoul 138-736, Korea
Tel +82-2-3010-3390
Fax +82-2-473-3725
E-mail tsko@amc.seoul.kr

*These two authors contributed equally in this work.

Introduction

Hemispherectomy has been recognized as an effective treatment modality for refractory epilepsy in children with hemispheric epileptogenic lesions. In 1938, McKenzie[1] introduced anatomical hemispherectomy for seizure control in infantile hemiplegia. Krynauw[2] subsequently reported successful seizure control in 10 of 12 cases in 1950. Anatomical hemispherectomy has subsequently become a widely used surgical approach for intractable epilepsy secondary to hemispheric syndrome such as in Rasmussen encephalitis, Sturge-Weber syndrome, hemimegalencephaly, and extensive hemispheric infarct.[3-5] Although this surgical technique has been associated with seizure-free rates of 70−80% in previous reports,[3,4,6] early and delayed surgical complications including hydrocephalus and superficial cerebral hemosiderosis have also occurred following this procedure, with associated high mortality rates.

To avoid these complications, functional hemispherectomy was introduced in 1983 by Rasmussen[6] based on a combina-

tion of the partial anatomic excision and disconnection of the remaining lobe. Furthermore, hemispherotomy incorporating partial cortical removal has reduced adverse events while still producing excellent results.[7-10] These technological improvements have widened the spectrum of congenital substrates of intractable epilepsy in childhood and highlighted the issue of seizure and cognitive outcomes in pediatric candidates.

The present study examined long-term seizure rates and functional outcomes in a series of pediatric patients with hemispheric disconnections who were treated at a single tertiary center in Korea. Detailed clinical characteristics and surgical techniques were also reviewed to evaluate outcome predictors.

Methods

We retrospectively reviewed the medical records of patients aged 18 years or younger who underwent a hemispherectomy or hemispherotomy between 1997 and 2005 at the Asan Medical Center. We collected demographic, clinical, imaging, and EEG data. All patients were confirmed as having intractable epilepsy secondary to hemispheric pathology by both a pediatric neurologist and a neurosurgeon. Presurgical evaluations included the family and personal histories, neurologic and neuropsychiatric examinations, 24-hour video EEG monitoring, and brain magnetic resonance imaging (MRI). Wada tests were performed in selected cases. We also collected data on the age at surgery, etiology of seizure, site of surgery, type of surgery, postoperative complications, postsurgical EEG, and brain MRI.

The final etiology of epilepsy was determined by preoperative brain MRI and postoperative histopathology. The postoperative seizure status was determined at the last follow-up or by telephone interview in cases lost to follow-up. Engel's classification was used to assess postsurgical seizure outcome. A neurological examination was performed by a pediatric neurologist at the last follow-up in order to quantify the functional outcome. The Korean version of the Wechsler Intelligence Scale for Children was used to evaluate cognitive outcome.

Results

Twelve pediatric epilepsy cases (8 males) treated at our hospital from 1997 to 2005 were reviewed. Their epilepsy onset age varied between 3 days and 7.6 years (mean, 3.0 years). The mean duration of seizure prior to surgery was 4.9 years (range, 0.6−11.2 years), and the mean age at surgery was 6.5 years (range, 0.8−12.3 years). All of the patients had symptomatic epilepsy with definite hemispheric etiologies: focal symptomatic epilepsy was described in 8 patients, West syndrome in 3 patients, and Rasmussen's syndrome in 1 patient following The International League Against Epilepsy classification (Table 1). Eight patients had a developmental pathology: five with focal cortical dysplasia, two with hemimegalencephaly, and one with Sturge-Weber syndrome. Four patients had an acquired pathology: two with encephalomalacia as a sequela of infarction, one with posttraumatic encephalomalacia as the result of a traffic accident, and one with Rasmussen's syndrome.

Three of our 12 patients had preoperative contralateral-side structural abnormalities on MRI that were associated with their diffuse pathologies. One patient showed cortical dysplasia as a sequela of congenital infection, one patient had posttraumatic encephalomalacia, and one had hemimegalencephaly showing contralateral structural lesions on brain MRI, but no contralateral EEG abnormalities. Preoperative interictal epileptiform abnormalities were identified in all 12 patients, but the affected hemisphere could be confirmed by ictal EEG in only 5 patients. Contralateral interictal discharges were also reported in three patients.

Surgical procedures and postoperative complications

Our study cohort received six functional hemispherectomies, two anatomical hemispherectomies, three peri-insular hemispherotomies, and one vertical parasagittal hemispherotomy. Five of these patients experienced early postoperative complications (<7 days after surgery). One child presented with acute brain edema, and the associated increased intracranial pressure was successfully treated using barbiturate coma therapy and osmotic diuresis. Two of our patients experienced aseptic meningitis, which improved by 2 weeks after surgery. Delayed postoperative complications (with an onset at >7 days postsurgery) including hydrocephalus or subdural hygroma requiring ventriculoperitoneal or subduroperitoneal shunts occurred in five patients. One of these cases developed a shunt-related brain abscess at 7 years postsurgery.

Table 1. Seizure outcomes according to etiology in the epilepsy cases of this study

Etiology	Seizure freedom (*n*=8)	Seizure persistent or recurrence (*n*=4)	Total (*n*=12)
Developmental pathology (*n*=8)			
Cortical dysplasia	4	1	5
Sturge-Weber syndrome	1	0	1
Hemimegalencephaly	0	2	2
Acquired pathology (*n*=4)			
Rasmussen's syndrome	1	0	1
Encephalomalacia (sequela of infarction)	1	1	2
Post-traumatic encephalomalacia	1	0	1

Seizure outcomes

During a long-term mean follow-up of 12.7 years (range, 7.6–16.2 years), eight of the 12 patients in our study cohort (66.7%) remained seizure-free (Engel class I) and one patient showed a >90% reduction in seizure frequency. Five patients (41.7%) were seizure-free after the surgery (Engel class Ia), with four of these cases achieving seizure freedom without the use of any antiepileptic drug (Table 2). The four remaining patients in our cohort (33.3%) continued to show persistent seizures or experience seizure recurrences (Engel class IIa or IIIa) (Table 3). Etiological seizure freedom occurred in four of our five patients with cortical dysplasia but in neither of the two patients with hemimegalencephaly.

Motor and cognitive outcomes

All of our patients except for one infant with generalized hypotonia exhibited pre-existing hemiparesis at the preoperative evaluation. Additionally, one of our patients had preoperative facial palsy and another exhibited limited extraocular movement before surgery. Despite a transient deterioration of hemiparesis during their early postoperative course, 11 patients were able to ambulate with or without an assistive device after surgery and no other neurological deterioration was reported at the last follow-up in all of these cases. One patient (patient 11) (Table 3) who underwent a vertical parasagittal hemispherotomy suffered postoperative intraventricular hemorrhage and hydrocephalus, and remained with spastic quadriplegia. However, the overall developmental severity category was unchanged following surgery in all of the patients in the current cohort (Table 2 and 3).

Discussion

Hemispheric disconnections have been reported to be efficient intervention approaches for epileptic seizures. These procedures are performed in children also to prevent additional cognitive injury to an otherwise healthy contralateral brain. However, defining the effect of hemispheric disconnections in children remains a challenge since there have been no randomized controlled trials of this method and the surgical candidates include a broad variety of epilepsy syndromes that arise at different ages.

To improve our understanding of the impact of hemispheric disconnections in children, we carefully reviewed the long-term outcomes of 12 pediatric epilepsy cases that underwent hemispheric disconnection at our hospital. In this case series, 75% of the children who underwent hemispheric disconnection became seizure-free or showed a >90% reduction in seizure frequency, which is consistent with the success rates reported for previously reported series of this type.[11-15] Although the etiologies, epilepsy syndromes, spectra of brain imaging abnormalities, and demographic data have differed among previous studies, hemispherectomy has been commonly reported as an effective treatment for intractable epilepsy. Recently, 136 of 186 hemispherectomized patients (73%) were reported to have achieved either seizure freedom or major reductions in seizure frequency.[13] In another study of 92 pediatric epilepsy patients, 78 of the cases (85%) were reported to be seizure-free at their last follow-up.[15]

Some previous studies have found that seizure outcomes differ significantly with the underlying etiology, and that they are significantly worse in epilepsy patients with a developmental pathology than in those with an acquired pathology.[7,11,16,17] In contrast, another study found no correlation between seizure outcome and etiology.[12] In our current pediatric series we found that seizure outcomes did not differ significantly between cases with developmental (5/8, 62.5%) and acquired (3/4, 75%) (Table 1) pathologies. However, neither of the two patients in our cohort with hemimegalencephaly achieved seizure freedom, whereas four of the five patients with cortical dysplasia achieved a seizure-free state. It has been found previously that the post-surgical seizure outcome and neurocognitive function were worse in patients with hemimegalencephaly than in those with other types of pathology.[5] A previous study found that although the rate of seizure freedom was 82.5% in acquired-pathology patients at a 3.4-year median follow-up, only one of the five patients in that series with hemimegalencephaly became seizure-free.[11] Similarly, the seizure-free rate in another 92 patients was worse in those with hemimegalencephaly (60%) than in patients with cortical dysplasia (80%).[15]

While the appropriate indication of hemispherectomy is expected to be a presentation with unilateral interictal and ictal EEG abnormalities, and structural brain lesions, some authors have argued that there is no relationship between the presence of contralateral EEG and brain MRI abnormalities and the seizure outcome.[12,18,19] In our current series, children with interictal epileptiform discharges in a contralateral lesion (patients 1 and 4) (Table 2) also achieved seizure freedom, in accordance with previous findings. Two of three patients in our present cohort with a preexisting contralateral brain MRI lesion–which was considered to be a nonepileptogenic focus (periventricular hyperintense signal or encephalomalacia)–became seizure-free after hemispheric disconnection. Because of the variable brain MRI lesions in such cases, some of which have uncertain clinical significance due to the dependence on the interpretation of the radiologist, various seizure outcomes for such lesions have been noted in previous studies.[12,20] Thus, the decision to proceed to hemisphere disconnection must be individualized based on various clinical features including the side of hemiparesis, semiology, lateralization findings on EEG, and the risk

Table 2. Seizure-free patients in this study after hemispheric disconnection: preoperative clinical characteristics and psychomotor outcomes

Patient	Etiology/ epileptic syndrome	Epilepsy onset (years)	Age at surgery (years)	Surgery type	Motor outcome (pre→post)	Development (pre→post)	Contralat. epileptiform discharge	Contralat. MRI abnormality	Postoperative complications	Seizure outcome (Engel class)	Antiepileptic drugs (pre→post)
1	CD/SFE	0.5	5.4	Lt. PIH	Rt. hemiparesis (grade IV) →no change	GDD→ND	Yes	No	No	Ia	PHT, VGB, VPA→none
2	RS/SFE	5.7	12.3	Rt. FH	Lt. hemiparesis (grade III) →no change	FSIQ=60 →FSIQ=60	No	No	Facial palsy	Ia	VGB, CBZ, VPA→none
3	EM after infarction/WS (Fig. 1A)	0.8	1.2	Lt. AH (Fig. 1E)	Rt. hemiparesis (grade IV) →no change	GDD→GDD	No	No	Hydrocephalus s/p VP shunt aseptic meningitis	Ia	VGB, TPM→none
4	CD/SFE (Fig. 1B)	0.7	9.2	Rt. FH (Fig. 1F)	Lt. hemiparesis (grade IV) →no change	ND→SQ=34	Yes	No	Hematoma at operative site	Ia	VPA, TPM, CBZ, CZP→none
5	Post-traumatic EM/SFE	4.8	10.5	Rt. AH	Lt. hemiparesis (grade IV) →no change	FSIQ=47 →FSIQ<40	No	Lt. frontal EM	Hydrocephalus subdural hygroma s/p VP shunt	Ia	CBZ, VPA, PHB→CBZ
6	SWS/SFE (Fig. 1C)	0.3	4.1	Rt. PIH (Fig. 1G)	Lt. hemiparesis (grade IV) →no change	GDD →FSIQ<34	No	No	No	Ib	PHB, VGB, LTG→PHB
7	CD/SFE	5.4	12.2	Rt. FH	Lt. hemiparesis (grade IV) →no change	FSIQ=80 →ND	No	No	Brain swelling	Ib	CBZ, VPA, CZP→CBZ, CLB
8	CD/SFE	4.4	6.7	Lt. PIH	Rt. hemiparesis (grade IV) →no change	GDD →FSIQ=50	No	PV HSI	No	Ib	TPM, CLB, VGB→TPM

AH: anatomical hemispherectomy, BA: background activity, CBZ: carbamazepine, CD: cortical dysplasia, CLB: clobazam, CZP: clonazepam, EM: encephalomalacia, FH: functional hemispherectomy, FSIQ: full scale intelligence quotient, GDD: global developmental delay, Lt.: left-side, LTG: lamotrigine, ND: no data available, PHB: phenobarbital, PHT: phenytoin, PIH: peri-insular hemispherotomy, PV HSI: periventricular high signal intensity, RS: Rasmussen's syndrome, Rt.: right-side, s/p: status post, SFE: simple focal epilepsy, SQ: social quotient, TPM: topiramate, VGB: vigabatrin, VP shunt: ventriculoperitoneal shunt, VPA: valproic acid, VPH: vertical parasagittal hemispherotomy, WS: West syndrome.

Table 3. Patients in this study who were refractory to hemispheric disconnection: preoperative clinical characteristics and psychomotor outcomes

Patient	Etiology/ epileptic syndrome	Epilepsy onset (years)	Age at surgery (years)	Surgery type	Motor outcome (pre→post)	Development (pre→post)	Contralat. epileptiform discharge	Contralat. MRI abnormality	Postoperative complications	Seizure outcome (Engel class)	Antiepileptic drugs (pre→post)
9	HME/SFE	7.6	9.0	Lt. FH	Rt. hemiparesis (grade IV) →no change	FSIQ=40 →FSIQ<45	No	No	Hydrocephalus s/p VP shunt	IIa	VGB, CBZ→VPA
10	EM after infarction/SFE	3.6	7.7	Lt. FH	Rt. hemiparesis (grade IV) →no change	SQ=34 →FSIQ<34	Yes	No	APOS, aseptic meningitis	IIIa	PHB, VGB, TPM→TPM, LEV, CLB, LTG
11	HME/WS (Fig. 1D)	2.3	2.6	Lt. VPH (Fig. 1H)	Rt. hemiparesis (grade IV) →spastic quadriplegia	GDD→ND	No	Mild brain atrophy	Hydrocephalus s/p VP shunt	IIIa	PHB, VGB, TPM→TPM, CLB, OXC
12	CD/WS	0.0 (3 days)	0.7	Lt. FH	Rt. hemiparesis (grade III) →no change	GDD→ND	No	No	Hydrocephalus s/p VP shunt	IIIa	VGB, TPM, LTG→LEV, CLB

APOS: acute postoperative seizure (occurring <7 days after surgery), CBZ: carbamazepine, CD: cortical dysplasia, CLB: clobazam, EM: encephalomalacia, FH: functional hemispherectomy, FSIQ: full scale intelligence quotient, GDD: global developmental delay, HME: hemimegalencephaly, LEV: levetiracetam, Lt.: left-side, LTG: lamotrigine, ND: no data available, OXC: oxcarbazepine, PHB: phenobarbital, Rt.: right-side, s/p: status post, SFE: simple focal epilepsy, SQ: social quotient, TPM: topiramate, VGB: vigabatrin, VPA: valproic acid, VPH: vertical parasagittal hemispherotomy, WS: West syndrome.

of a new prospective neurologic deficit.

Almost all of the children in our current series exhibited pre-existing hemiparesis, and the symptoms remained unchanged following surgery in all cases despite a transient worsening of the hemiparesis during the early postoperative period. Previous related findings are concordant with our current results, which suggests that hemiparesis is likely to remain unchanged in the majority of cases, with few patients likely to show either an improvement or a deterioration.[2,4,11] Despite a young age at surgery and the achievement of walking with support after surgery, an infant in our present series who was hypotonic at the time of surgery was hemiparetic at the last follow-up. Considering the motor complications in that case, this finding suggests that a decision to undergo a hemispheric disconnection may be much easier to make if the patient has pre-existing hemiparesis.

Cognitive development was substantially interrupted among all of the children in our cohort with severe epilepsy, particularly in cases with symptomatic epilepsy. All of the children examined in this study had a hemispheric malformation or traumatic lesions and had exhibited cognitive and developmental delay prior to surgery. The developmental and cognitive status of these patients did not deteriorate after surgery, and most of these individuals showed unchanged intelligence or developmental levels. It has also been previously reported that preoperative neurocognitive function is one of the most important determinants of postoperative cognitive function.[11,12,21,22] These findings support that early surgical intervention can stabilize the cognitive function of the remaining hemisphere by arresting further seizures, even though the already impaired cognition cannot be regained. However, complete seizure control or elimination of traumatic seizures can improve the daily living activities and greatly improve the quality of life, which can be another important purpose of epilepsy surgery in children.

Despite its enormous efficacy against intractable seizures with hemispheric lesions, the postoperative complications of hemispheric disconnection procedures such as blood volume loss, intracranial hematoma, hydrocephalus, and superficial hemosiderosis are critical aspects of this procedure that can severely affect the associated morbidity and mortality. Some of our patients experienced aseptic meningitis, brain swelling, and intracranial hematoma during the early postoperative period, or hydrocephalus requiring a shunt operation. All of the four children in our present cohort who had poor seizure outcomes had also experienced surgical complications, which strongly suggests an association between adverse events following surgery in epileptic patients and the seizure outcome.

To further decrease adverse events following such surgery, a new surgical procedure that is based on hemispherotomy has been developed that reduces the volume of brain removed and increases the ratio of disconnection to resection.[23] Various

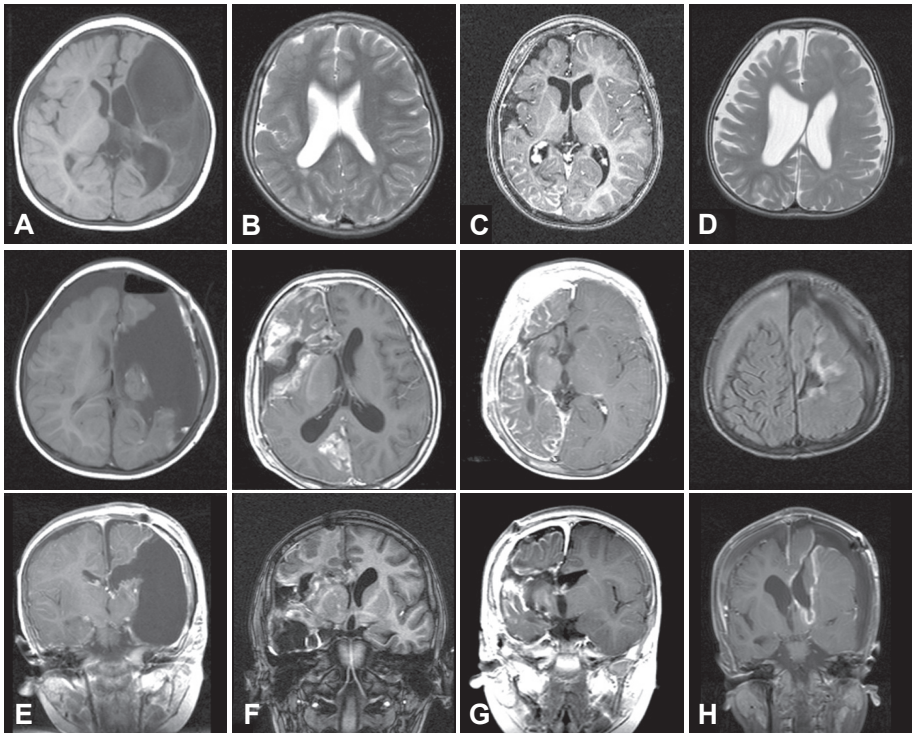

Fig. 1. Presurgical MRI scans of patients with different etiologies (A-D). Left encephalomalacia (patient 3) (A), right frontotemporal cortical dysplasia (patient 4) (B), Sturge-Weber syndrome involving the right hemisphere (patient 6) (C), and left hemimegalencephaly (patient 11) (D). Axial (upper) and coronal (lower) MRI scans demonstrating the main surgical procedure for hemispheric disconnection (E-H). Anatomical hemispherectomy produced by removal of the entire hemisphere including most of the deep structures in patient 3 (E). Functional hemispherectomy based on a combination of partial anatomic excision and disconnection of the remaining lobes in patient 4 (F). Modified peri-insular hemispherotomy and removal of the frontotemporoparietal operculum and underlying deep structures in patient 6 (G). Vertical parasagittal hemispherotomy performed in patient 11 (H).

modifications of hemispherotomy have been described,[7,8] and the following four different surgical procedures were used for hemispherotomy in our current series by a single neurosurgeon (JKL): functional hemispherectomy (n=6), anatomical hemispherectomy (n=2), peri-insular hemispherotomy (n=3), and vertical parasagittal hemispherotomy (n=1). All of these surgical procedures included callosotomy and disconnection of the frontal and occipital lobes. Anatomical hemispherectomy involves the complete removal of the hemisphere whilst sparing the thalamus and basal ganglia. Functional hemispherectomy involves a temporal lobectomy, resection of the frontoparietal cortex, callosotomy, and disconnection of the residual frontal and parieto-occipital lobe. Peri-insular hemispherotomy consists of insular resection or dissection through the supra- and infra-insular windows, and transventricular callosotomy through the window. A temporal lobectomy was performed during the infra-insular window stage. Vertical parasagittal hemispherotomy is a modified surgical technique that reaches the lateral ventricle through a vertical parasagittal plane (Fig. 1). The type of surgery was carefully chosen for each patient through a multidisciplinary management consultation process based on the consideration of multiple factors, including etiology, extent of brain abnormalities, and EEG findings.

Our retrospective review of a small pediatric cohort was subject to several noteworthy limitations. The small number of patients included in the review prevented an analysis of the correlation between clinical factors and outcomes. A lack of standardized functional outcome measures obscured the consistent assessment of cognitive and motor function. However, the long-term seizure outcomes of hemispheric disconnection in our selected patients was excellent and provides valuable information that should help in the future to prevent intractable seizures in children with a hemispheric pathology.

In conclusions, we have found hemispheric surgery to be a potent treatment option for children with medically intractable hemispheric epilepsy. This procedure can lead to seizure-free outcomes without significant neurocognitive deterioration. Optimizing seizure outcomes requires the selection of appropriate candidates for hemispheric disconnection and application of the most suitable surgical technique for these patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

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