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Review article

Epilepsy surgery for hemispheric syndromes in infants: Hemimegalencepahly and hemispheric cortical dysplasia ☆

Christine Bulteau [a,c,*], Taisuke Otsuki [b], Olivier Delalande [c]

[a] *Inserm, U663, Paris Descartes University, Sorbonne Paris Cité, F-75015 Paris, France*
[b] *Epilepsy Center, National Center of Neurology and Psychiatry, Tokyo, Japan*
[c] *Foundation Ophtalmologique A. de Rothschild, Pediatric Neurosurgery Department, F-75019 Paris, France*

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Abstract

Objective: Hemimegalencepahly (HME) and Hemispheric Cortical Dysplasia (HCD) are rare congenital diseases that occur with intractable epilepsy. They manifest by early epilepsy, mental retardation, hemianopsia and contralateral hemiplegia. Hemispheric disconnection (mainly anatomical hemispherectomy, peri-insular hemispherotomy, modified lateral hemispherotomy and vertical parasagittal hemispherotomy) have been reported to be efficient on seizures and also to prevent additional cognitive injury and developmental delay. *Method:* We reviewed literature about clinical presentation, predictors of outcome and expectation about epileptic seizures and cognitive outcome. *Results:* Clinical presentation and seizures outcome have been described in almost 600 children for the last thirty years. Epilepsy improved in most cases depending on the series and the follow-up duration. Percentage of seizure-free patients with HME or HCD was lower than in other groups (Rasmussen Encephalitis, Vascular Sequellae). Post-operative complications decreased with the hemispherotomy surgical procedures. EEG abnormalities on the "save" hemisphere did not negatively influence postsurgical outcome. Seizure free outcome did not seem to depend on the surgical procedure but the presence of residual insular cortex seemed to be associated with persistent postoperative seizures. Contralateral MRI abnormalities seemed to be associated with poorer prognosis for seizure free outcome and lack of cognitive improvement. *Conclusion:* Hemispheric disconnection remains the best treatment in order to control epileptic seizures. Hemispheric surgical procedures are safe and can be performed from the first month of life. Prospective studies of cognition are needed to emphasize benefits on long term outcome.

Keywords: Hemimegalencephaly; Hemispheric cortical dysplasia; Hemispherotomy; Prognosis

1. Introduction

Presurgical evaluation is highly recommended in children with intractable focal epilepsy and lesional hemispheric epilepsy since epilepsy surgery remains a good opportunity to cure epilepsy or decrease seizure frequency and burden of co-morbidity factors [1,2]. Although surgical procedures have evolved over the last twenty years, there are not enough Class I and II data to formulate surgical guidelines. Each year more than 500 children undergo epilepsy surgery, and among them 20% present with hemimegalencephaly or hemispheric cortical dysplasia [3].

Hemimegalencepahly (HME) and Hemispheric Cortical Dysplasia (HCD) are rare congenital and sporadic diseases that occur with early intractable epilepsy,

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* Corresponding author. Address: Fondation Ophtalmologique A. de Rothschild, Pediatric Neurosurgery Department, 25–29 rue Manin, 75940 Paris Cedex 19, France. Tel.: +33 1 48036817; fax: +33 1 48036562.
E-mail address: cbulteau@fo-rothschild.fr (C. Bulteau).

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mental retardation and neurological hemideficit (contralateral hemianopsia and hemiplegia). Seizures occur in the first days of life in 85% of children. They consist of partial motor seizures, asymmetric tonic or clonic generalized seizures mostly in series involving predominantly one side of the body, contralateral to the damage. The EEG shows various abnormal patterns, characterized by suppression-burst and/or hemihypsarrhythmia over the malformed hemisphere, a rather high-frequency background activity associated with hemispheric continuous or repetitive spikes, sharp waves and spike and waves that progressively involve the contralateral hemisphere [4–6]. Some interictal EEG patterns are quite specific of HME and should be recognized easily in order to orient diagnosis and early surgery. Bilateral EEG abnormalities are common in children with malformations of cortical development, more often on interictal than ictal records. The prognosis of these severe unilateral brain malformations may be improved by hemispheric disconnection [2,4]. The first case of hemispherectomy for a child with HME was reported by King et al. [7] with a favourable outcome. Moreover, epilepsy surgery may prevent additional cognitive injury, developmental delay and epileptic encephalopathy [8].

Defining the spectrum of epilepsy surgery for hemispheric syndrome in infants remains a challenge since there is no randomized controlled trial. Our goal was to summarize level of available data in infants with hemispheric syndrome.

2. Method

We reviewed the literature regarding clinical presentation, surgical procedure and expectation about epileptic seizures and cognitive outcome in infants with hemispheric syndrome. Clinical presentation, seizures and post-operative and cognitive outcome have been reported in over 500 children during the last thirty years. Most publications report few patients and we took in account only those with at least 10 cases undergoing hemispheric disconnexion (Table 1). According to these publications and the focus of the study, we pointed out knowledge of available data in four domains: etiology, surgical procedure, seizure outcome and predictive factors.

3. Results

3.1. Etiology

Diagnosis of hemispheric syndrome required brain MRI which revealed multilobar cortical dysplasia, HME, polymicrogyria, with some typical features: abnormal gyral formation, abnormal cortical thickness, loss of gray matter differentiation, abnormal signal on T2–weighted image [9].

HME is quite typically characterized by the enlargement of one hemisphere often associated with abnormal gyration, thick cortex, ventricular asymmetry, abnormal gray–white matter differentiation, neuronal heterotopia and basal ganglia and internal capsule abnormalities [8,10]. The most common histological patterns included architectural disorganization, increased molecular layer patterns, neuronal cytomegaly, hyperplasia of glia cells with giant astrocytes [11–13]; ectopic and large neurons with abnormal cortical lamination which may be responsible for the MRI characteristics [9].

HME is often an isolated syndrome but it has been described as an occasional feature of a large number of syndromes many of which may not be readily identified at birth. Case series and reports of HME are associated with neurocutaneous syndrome (hypomelanosis of Ito, Tuberous sclerosis, neurofibromatosis, epidermal naevus syndrome, Klippel–Trenonay–Weber syndrome, organic naevus syndrome) and/or with known or suspected genetic anomaly [6,14–16] in almost half of the patient. There is no familial occurrence or sex difference (Table 2).

3.2. Surgical procedure

Hemispheric disconnection surgical procedure (mainly anatomical hemispherotomy, peri-insular hemispherotomy, modified lateral hemispherotomy and vertical parasagittal hemispherotomy) have been reported (Fig. 1) to be efficient on seizures [2,4] and also to prevent additional cognitive impairment. Cook et al. [17] exhibited immediate post-operative complications such as considerable intraoperative blood loss with the classical procedure of anatomical hemispherectomy as well as functional hemispherectomy. It is worth mentioning that HME patients had the greatest perioperative blood loss and the longest surgery time. Another surgical procedure based on a combination of partial anatomical excision (hemidecortication and functional hemispherectomy) was introduced but the efficiency on seizure control was diminished especially in the group of children with diffuse cortical dysplasia since these techniques spared insular cortex or as much as possible white matter mixed with heterotopia. Finally, the hemispherotomy technique offers various advantages in children with hemispheric syndrome. In order to further decrease complication rates, these new surgical procedures have been developed, reducing the volume of brain removal and increasing the ratio of disconnection to resection. They require a smaller skin incision and bone flap which offers the advantages of reducing blood loss and avoiding the exposure of large venous sinuses. Various modifications of the hemispherotomy have been described: the peri-insular hemispherotomy [18], the so called "modified lateral hemispherotomy" [17] and the vertical parasagittal hemispherotomy [19]. Lateral hemispherotomy is more difficult to perform in children born with

Table 1
Articles with more than 10 cases reported to have hemispheric syndrome (HME and HCD).

Author	Year	*N*	Engel 1	Surgical procedure	Mean follow-up	Focus
Battaglia et al.	1999	10 HME	60%	A	63 months	Improved QOL/Good pre-operative development is associated with better prognosis
Boshuisen et al.	2010	18	88%/ 45%	F	ND	Sz freedom depended on controlateral MRI abnormalities
Carreno et al.	2001	12	17%/ 83%	F	19.3 months	Sz freedom depended on extensive subcortical heterotopic gray matter (HME) not disconnected after functional hemispherotomy
Cats et al.	2007	10	90%	F	39 months	Sz freedom depended on residual insular cortex
Cook et al./Jonas et al.	2004/ 2004	55	70%/ 45%	A/F/Mod Lateral H	12 months/ 60 months	Peri-operative risk and hospital course varied by hemispherotomy techniques/Post surgery autonomy correlated with sz duration, sz contrl and presurgery development but not post-surgery control
Curtiss et al.	2001	19	42%	A	72 months	Sz freedom correlated with better cognitive outcome
Delalande et al.	2007	30	63%	Vertical Parasagital H	52 months	Vertical hemispherotomy was a safe technique/Longer the duration of epilepsy, lower the communication skills
Devlin et al.	2003	16	31%	A	40 months	Sz freedom depended on etiology: porrer with developmental pathology
Di Rocco et al.	1994/ 2000	15 HME	60%	A	46 months	Age (<9 months) plays an important role in the occurrence of secondary hydrocephalus
Gonzalez-Martinez et al.	2005	16	60%	A/F/Mod A H	34.8 months	Early surgery (<2 years of age) should be indicated/expert team for pediatric epilepsy surgery is mandatory
Holthausen et al.	1997	103	57%	A/F/VPH/Adams modification/Hdecort	6 months	Sz outcome with respect to surgical technique (Hemispherotomy and Adam'smodification having the best results) and to etiology (dyplasia worse results)
Hallbook et al.	2010	43	72%	A/F	24 month	Contralateral MRI finding did not correlate with Sz freedom and may not contraindicate hemispherectomy
Kwan et al.	2010	20	48%/ 85%	Hdecort/PIH	72 month	PIH tended to have fewer complications, more favorable outcome and decreased need for subsequent surgical procedure
Limbrick et al.	2009	18	70%	F/PIH	29 months	H was efficient for Sz control and worthwhile improvment/Bilateral EEG abnormalities may be predictive of postH Sz recurrence
Maehara et al.	2000	11	45%	F	26 months	FH may result in remarkable seizure reduction and psychomotor improvment
Pulsifer et al.	2004	27	44%	A	64 months	The most significant predictor of cognitive outcome factor was etiology with dysplasia patients scoring lowest
Salamon et al.	2006	23 HME	68%	A/F/Mod F	52 months	In 11 HME and 6 non HME/Poorer post-surgery seizure control and cognitive outcomes were due to contralateral hemimicrencephaly
Sasaki et al.	2005	11 HME	72%	F	ND	Survey of Japanese patients 44HME / Correlation between age of Sz onset and severity of motor deficit and intellectual level
Shimizu et al.	2005	31	30%/ 80%	Mod PIH	ND	Sz depend on etiology (30% for HME and 80% for HCD)/incomplete disconnection of the corpus callosum can cause surgical failure
Vining et al.	1997	24	67%	A	66 months	Early H relieved the burden of constant Sz and allowed the resumption for more normal development

A = anatomical, F = functional, Mod = modified, H = hemisphrotomy, Hdecort = hemidecortication, PI = peri-insular.

Table 2
Underlying syndrome associated with HME.

Author	*N*	%	Syndromic
Di Rocco et al. (2000)	7 (15)	47	Hemifacial gigantism/neurocutaneous syndrome: hypomelanosis of Ito, TS, NF, epidermal naevus syndrome, Klippel–Trenonay–Weber syndrome
Sasaki et al. (2005) Epidemiological study in Japan	16 (44)	36	Neurocutaneous syndrome: epidermal nevus syndrome (Linear nevus syndrome/sebaceous nevus syndrome), hypomelanosis of Ito, TS complex, Klippel–Trénaunay–Weber syndrome
Tinkle et al. (2005)	7 (15)	47	Body hemi-hypertrophy (ipsilateral)/other unilateral congenital somatic abnormalities: polycystic kidney disease, hypothyroidism, multiple angiomyolipomas Neurocutaneous syndrome: epidermal nevus, linear nevus sebaceum

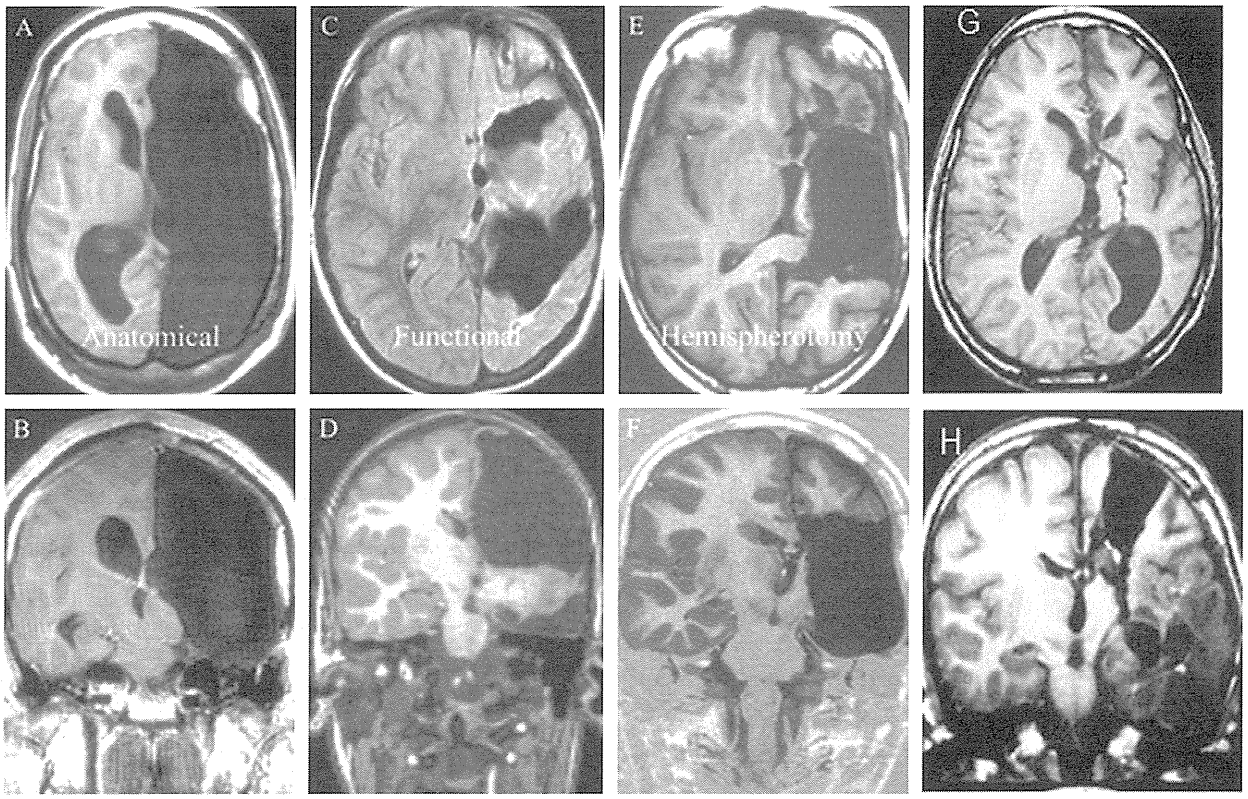

Fig. 1. Axial (upper) and coronal (lower) MRI scans demonstrating the main surgical procedure for hemispheric disconnexion; (A–F) belong to Cook et al. (2004), (G) and (H) belong to Delalande et al. (2007). (A and B): Anatomical hemispherectomy produced by removal of the entire hemisphere including most of the deep structures of the basal ganglia, thalamus, and caudate nucleus. (C and D): Rasmussen functional hemispherectomy based on a combination of partial anatomic excision (insular cortex and basal ganglia are not resected) and disconnection of the remaining lobes. *To further decrease complication rates after hemispherectomy, new surgical procedures have been developed that reduce the volume of brain removal and increase the ratio of disconnection to resection and was called hemispherotomy.* (E and F): modified lateral or peri-insular hemispherotomy removes a block of tissue that includes the fronto-temporo-parietal operculum and underlying deep structures. (G and H): vertical parasagittal hemispherotomy the incision around the central core (consists of the extreme, external, and internal capsules, claustrum, lentiform and caudate nuclei, and thalamus) respecting the same section as in anatomic hemispherectomy with preservation of an intact vessel supply.

cerebral malformation (hemimegalencephaly or cortical dysplasia) than VPH because of abnormal brain parenchyma and ventricular anatomy.

3.3. Expectation for outcome

The prognosis of these severe unilateral brain malformations may be improved by hemispheric disconnection surgical procedure.

3.3.1. Seizures

The epilepsy improved in most cases and the amount of seizure-free patients depends on the series and the follow-up duration (Table 1). It is admitted that among the groups of patients undergoing hemispheric disconnection, seizure outcome is poorer in developmental hemispheric patients.

Although the incidence of pre-operative bilateral EEG abnormalities is quite common in children with

cortical developmental malformation, these findings alone should not preclude further consideration for hemispheric disconnection [20]. Some studies have demonstrated that bilateral EEG abnormalities may be predictive of post-hemispherotomy recurrent seizures [21] but others do not [20]. Finally, Smith et al. [22] pointed out that bilateral independent epileptogenic foci indicate a less satisfactory outcome: in contrast abnormalities of background activity over the good hemisphere or bilaterally synchronous discharges were associated with a good outcome.

Pre-operative MRI is also recognized as a predictive factor for seizure outcome. Some studies have pointed out that abnormal hemispheres with extensive insular and subcortical heterotopic gray matter are not completely disconnected by functional hemispherectomy [23,24]. Even if seizure free outcome does not depend on the surgical procedure, hemispherotomy techniques are highly recommended when insular and subcortical abnormalities are present [25]. Moreover, contralateral MRI abnormalities are frequent in children with malformation of cortical development, affecting 25–72% according to the studies, and the impact on seizure control is still debated [26,27]. Nevertheless, contralateral abnormalities may not contraindicate hemispherotomy in order to decrease seizure frequency. Salamon et al. [13] proposed that poorer post-surgery seizure control and cognitive outcomes are due to contralateral hemimicrencephaly in most HME patients.

3.3.2. Cognition

After hemispheric disconnection, the patient has to deal with growing and learning with a single hemisphere. Then all the neurological events which are able to impair the non-operated hemisphere have to be taken in account in the cognitive outcome. Some predictive factors for cognitive outcome have been already identified. A long duration of epilepsy before surgery is associated with bad prognosis on global outcome [28], especially on verbal communications abilities [19]. Since catastrophic epilepsy is characterized by discharges spreading from the malformed hemisphere to the "healthy" hemisphere [29,30], the non-malformed hemisphere is impaired within the first months of epilepsy preventing cognitive plasticity mechanisms which can be restored after hemispheric disconnexion. Post-surgery seizure control correlated positively with spoken language outcome in children with developmental etiology compared with acquired pathology [31].

The overall prognosis of HME patients is heterogeneous and early prediction of outcome is important. A worse outcome in cognitive function of HME patients is suspected to be related to contralateral hemispheric dysfunction. Abnormal metabolism as well as MRI abnormalities of the non HME hemisphere is associated with lower or lack of post-operative cognitive improvement [32,26]. These findings are consistent with prospective cognitive findings reported by Battaglia et al. [33] who pointed out a better cognitive outcome when pre-operative neuropsychological assessment was good and when there was less severe morphological and functional changes over the "healthy" hemisphere. Other studies demonstrated that etiology is the most significant predictor for cognitive skills with dysplasia patients scoring lowest in intelligence and language [34].

3.3.3. Motor

The neurological deficit did not increased after surgery [33]. Spasticity of the hemiparetic side is less severe in the long-term outcome in children with developmental disorder compared to those with acquired pathology [19]. For the great majority of patients residual motor control is more severely impaired for hand functions than for walking. Nevertheless, functional motor outcome differed according to etiology and children with developmental disorder underperformed children with perinatal stroke [35].

4. Conclusion

Epilepsy surgery is recommended in infants with catastrophic epilepsy associated with hemimegalencephaly and hemispheric cortical dysplasia. Hemispheric disconnection surgical procedures are proposed in order to control epileptic seizures and try to avoid encephalopathy. Etiologies are numerous but HME is quite typical frequently associated with neurocutaneous syndrome. Hemispherotomy techniques offers various advantages related to operative blood loss and reoperation compared with anatomical and functional hemispherectomy. The prognosis for seizure and cognitive outcome after hemispheric disconnection is poorer in this population compared to other etiologies since bilateral cortical malformation is suspected in some patients.

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CASE REPORT

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Posterior Disconnection in Early Infancy to Treat Intractable Epilepsy With Multilobar Cortical Dysplasia

—Three Case Reports—

Qin-Chuan LIANG,[1] Taisuke OTSUKI,[2] Akio TAKAHASHI,[2] Takashi ENOKIZONO,[3] Takanobu KAIDO,[2] Yuu KANEKO,[2] Eiji NAKAGAWA,[3] Kenji SUGAI,[3] and Masayuki SASAKI[3]

[1]*Department of Neurosurgery, Tangdu Hospital, The Fourth Military Medical University, Xi'an, China;*
Departments of [2]*Neurosurgery and* [3]*Child Neurology, National Center Hospital of Neurology and Psychiatry, National Center of Neurology and Psychiatry, Kodaira, Tokyo*

Abstract

Extensive multilobar cortical dysplasias occasionally occur in children and can induce seizure onset in early infancy, causing severe epileptic encephalopathy. Surgical interventions in early infancy, such as disconnection of large parts of the brain, are challenging because of the degree of invasiveness and carry greater risks in infants compared with older children. Here we report the successful treatment of intractable epilepsy with multilobar cortical dysplasias in the posterior cortex by posterior disconnection in three infants (age 3 months). The patients showed good postoperative recovery and exhibited excellent seizure control at follow-up evaluation within a year after surgery. Developmental catch-up was also achieved and no early complications have been detected to date. Use of the posterior disconnection technique for early-stage extensive multilobar cortical dysplasias can result in good seizure control and developmental progress with little perioperative morbidity. However, the efficacy of this surgical technique needs to be verified with long-term follow up after surgery.

Key words: epilepsy, cortical dysplasia, posterior disconnection

Introduction

Children with extensive multilobar cortical dysplasias (MCDs) frequently present with seizure onset in early infancy, ultimately resulting in severe epileptic encephalopathy.[5,13] Although early surgical intervention is necessary to control epilepsy and allow normal brain development, conventional resective surgery, which involves the removal of large parts of the cerebral hemisphere, is challenging and carries substantial operative risks in infants compared with older children.[17,20] Similar to the evolution of hemispherectomy, surgical techniques for epilepsy with MCDs has advanced toward more disconnection and less resection to minimize perioperative complications.[4,5] In addition to minimizing complications, maximizing the suppression of epileptic seizures is a primary goal of surgical intervention. We report here the successful treatment of three infants with intractable epilepsy resulting from MCDs in the posterior cortex by posterior disconnection with an optimal therapeutic strategy based on multimodal examinations.

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Case Reports

Case 1: A 3-month-old boy born at term after an uneventful pregnancy presented with generalized tonic seizures with eye deviation to the left side, beginning 6 days after birth. The frequency of seizures was 10–40/day. Seizures were intractable to multiple anticonvulsants (phenobarbital 35 mg/day, clonazepam 0.24 mg/day). His development was significantly delayed with a developmental quotient (DQ) of 60. Magnetic resonance (MR) imaging showed an increase in the volume of the right temporal, parietal, and occipital lobes compared with the contralateral side. In addition, poor differentiation was observed between gray and white matter in the right temporal, parietal, and occipital lobes. These radiological findings suggested temporo-parieto-occipital cortical dysplasia (Fig. 1A, B).

Interictal single photon emission computed tomography (SPECT) showed decreased cerebral blood flow (CBF) in the right temporal, parietal, and occipital lobes. Ictal SPECT showed relative hyperperfusion in the right temporal, parietal, and occipital lobes (Fig. 1C). Subtraction ictal SPECT coregistered with MR imaging (SISCOM) showed that significant ictal hyperperfusion was

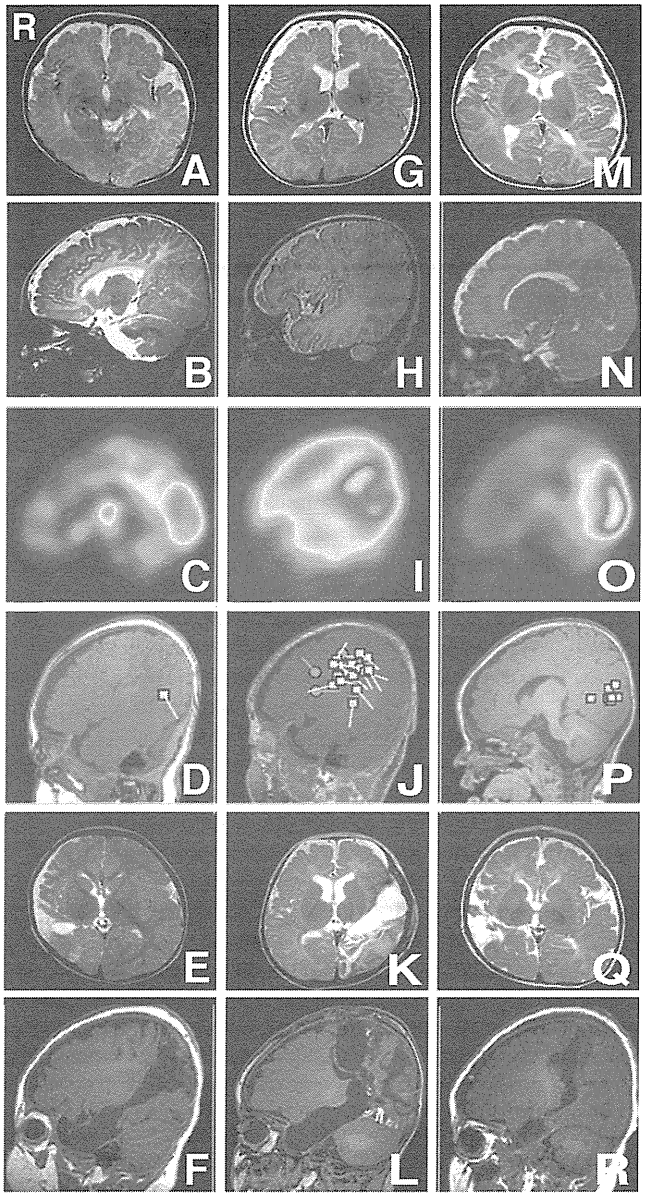

Fig. 1 Neuroimages of Case 1 (A–F), Case 2 (G–L), and Case 3 (M–R). A, B, G, H, M, N: Magnetic resonance (MR) images demonstrating temporoparietooccipital cortical dysplasias. C, I, O: Ictal single photon emission computed tomography scans. D, J, P: Magnetoencephalography with superimposition onto sagittal MR images. E, F, K, L, Q, R: Postoperative axial and sagittal MR images showing the site of posterior disconnections.

predominantly observed in the lateral part of right temporal lobe. Magnetoencephalography (MEG) revealed spike dipoles in the occipital lobe and the transitional area between the occipital and temporal lobes (Fig. 1D). Interictal electroencephalography (EEG) showed bilateral occipital-dominant large δ waves and θ waves and frequent spikes over the right occipital, temporal, and posterior temporal areas. The ictal EEG was characterized by bilateral occipital dominant polyspike spreading over the right cerebral hemisphere (F8, T6, P4, O2).

The aim of the surgery was to eliminate the influence of the large dysplastic epileptogenic zone comprising the temporal, parietal, and occipital lobes. The patient underwent right parieto-occipital disconnection and temporal lobectomy with no postoperative complications. Postoperative EEG (2 months after operation) showed localized epileptic waves in the disconnected right temporal lobe. At the latest follow-up review, a year after surgery, the patient was seizure free and had achieved developmental catch-up with a DQ of 73.

Case 2: A 3-month-old girl born at term after an uneventful pregnancy presented with tonic seizures and epileptic spasms with asymmetric tonic posture and eye blink and deviation to the left side, beginning 13 days after birth. The frequency of seizures was 10–40/day. Seizures were intractable to multiple anticonvulsants (zonisamide 120 mg/day, phenobarbital 56 mg/day). Her development was significantly delayed with a DQ of 44. MR imaging showed a diffuse lesion in the left temporo-parieto-occipital lobe. Axial images revealed that abnormal gray matter extended from the trigone of the lateral ventricle to the occipital cortex and extended anterior to the central sulcus and insular cortex (Fig. 1G). Ictal SPECT revealed relative hyperperfusion in the transitional area between right temporal, parietal, and occipital lobes (Fig. 1I). MEG showed spike dipoles in the area around the angular gyrus (Fig. 1J). Interictal EEG revealed lateralized epileptic discharges on the left. Ictal EEG was characterized by unilateral spike-wave activities spreading over the left hemisphere (P3, O1, T5, T3).

The patient initially underwent right posterior disconnection. After the first surgery, seizures persisted. Judging from the postoperative MEG and SISCOM findings, the seizures were considered to arise from the residual parieto-temporal operculum, the posterior insular cortex, and temporal lobe. Additional resection of those cortices were performed 40 days later. There were no postoperative complications. Postoperative EEG (2 months after operation) revealed localized epileptic waves in the right temporal lobe. At a follow-up evaluation 5 months after surgery, the patient was seizure-free and had made developmental progress with a DQ of 50.

Case 3: A 3-month-old boy born at term after an uneventful pregnancy presented with seizures consisting of epileptic spasms with eye deviation to the left side, beginning 10 days after birth. The frequency of seizures was 20–30/day. Seizures were intractable to multiple anticonvulsants (carbamazepine 120 mg/day, lamotrigine 4 mg/day, zonisamide 60 mg/day). His development was normal with a DQ of 117. MR imaging showed an increase in the volume of the transitional area of the right temporal, parietal, and occipital lobes. Poor differentiation was observed between gray and white matter in the abnormal area (Fig. 1M, N). Interictal SPECT revealed increased CBF in the right occipital lobe (Fig. 1O). MEG showed dipoles in the right occipital and temporal lobes (Fig. 1P). Interictal EEG showed lateralized epileptic discharges on the right. Ictal EEG was characterized by unilateral spike-wave activity spreading over the right hemisphere (C4, P4,

T6). The patient underwent posterior disconnection with no postoperative complications. Postoperative EEG (one month after operation) revealed localized epileptic waves in the disconnected right temporal lobe. At a follow-up evaluation 6 months after surgery, the patient was seizure-free with normal development.

Surgical Procedure and Outcome

During the operations, electrocorticography was performed over the exposed cortices and the locations of the central and postcentral sulci were identified in relation to known anatomic landmarks on MR imaging. Anterior temporal lobectomy was carried out, including resection of the amygdala and the anterior hippocampus up to the level of the choroid fissure (Fig. 2B). The temporal and parietal opercular cortices were removed to make the periinsular window (Fig. 2A). The opening of the ventricle was extended in the posterior direction to the trigone of the lateral ventricle. Parenchymal resection was performed from the posterior limit of the temporal cortical resection to the postcentral sulcus, upward along the parietal lobe, and finally, to the corpus callosum (Fig. 2C–E). Transventricular posterior callosotomy was carried out in a intraventricular parasagittal plane posterior to the intraparietal disconnective line (Fig. 2C). This procedure would interrupt all the parieto-occipital commissural fibers as they reach the corpus callosum. After the splenial disconnection, incision reached the fornix. The fornix is then incised to disconnect the posterior hippocampus. Finally, the electrocorticography was re-recorded and no spikes were observed in the remaining temporal, occipital, and parietal lobes.

The brain tissues harvested from surgery revealed structural abnormalities consistent with MCDs. The cerebral cortex did not achieve its normal architecture. Accumulation of numerous balloon cells was present throughout the whole cerebral cortex and in the underlying white matter.

Discussion

Children undergoing epilepsy surgery more often exhibit extratemporal lesions compared with temporal lesions, which are more common in adults. In addition, cortical dysplasia is the most frequent etiology. Extratemporal and multilobar cortical resections for intractable epilepsy are much more common in pediatric patients compared with adult patients.[9,12] In some cases of medically intractable pediatric epilepsy, the extent of the underlying cortical abnormality requires hemispherectomy[14]; however, in others, the epileptogenic focus is more limited, involving one or more lobes of one hemisphere. The pathological profile in the cases presented here involved malformations of cortical development, and all patients were diagnosed with catastrophic epilepsy, characterized by seizure onset within 2 weeks of birth and high frequency of seizures (10–40/day). The concept of "intrinsic epileptogenicity" may account for the medical intractability, incidence of status epilepticus, and the persistence of epilepsy after incomplete removal of the dysplastic zone.[18] It may be that

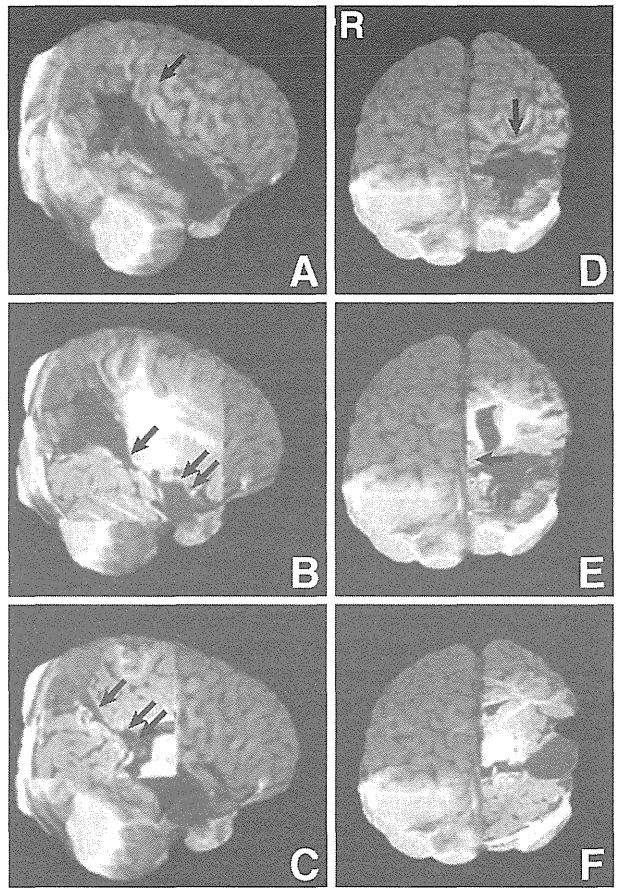

Fig. 2 Postoperative three-dimensional surface rendering magnetic resonance images in Case 1. A–C: Lateral view; D–F: axial view; B, C, E, F: cut-out images of the brain (right upper quadrant). A: Surface rendering image showing the periinsular window. The temporal pole, the temporal opercular cortex, and the parietal opercular cortex were resected. The *arrow* indicates the central sulcus. B: Cut-out image demonstrating mesial temporal resection and posterior hippocampotomy. The *arrow* indicates the site posterior hippocampotomy was performed. The *paired arrow* shows resection of the amygdala and the anterior hippocampus. C: Cut-out image demonstrating intraventricular posterior callosotomy and interparietal disconnection. The arrow indicates the site interparietal disconnection was performed. The *paired arrow* shows posterior callosotomy. D: Surface rendering image showing the interparietal disconnection. The *arrow* indicates the central sulcus. E: Cut-out image demonstrating intraventricular posterior callosotomy. The *arrow* indicates the site posterior callosotomy was performed. F: Cut-out image demonstrating mesial temporal resection and posterior hippocampotomy.

the extent of the malformation explains the high association between MCDs and catastrophic epilepsy.[20] These ideas support the diagnoses of catastrophic epilepsy in our cases, because of the huge cortical dysplasias observed and because the patients were seizure-free after complete disconnection of MCDs.

Posterior disconnection is indicated when the epileptogenic zone encompasses large areas of the temporal,

Table 1 Literature review of multilobar cortical dysplasia (MCD) surgery series

Author (Year)	No. of patients	Age group	Seizure type (no. of patients)	MR imaging findings (no. of patients)	PET metabolism	Ictal SPECT	Scalp EEG	Operation	Outcome
Chugani et al. (1993)	11	infant	ES (7), other (4)	HM (1), MCDs (1), pachygyria (1), normal (9)	↓ in 9/11, ↑ in 2/11	not done	concordant in 11/11	all resection	10/11 SF (91%)
Wyllie et al. (1996)[20]	2	child	tonic (1), ES (1)	MCDs (2)	↓ in 2/2	not done	concordant in 1/2	all resection	2/2 SF (100%)
Leiphart et al. (2001)[12]	24	child	no details	CD (15), gliosis (6), TS (1), encephalomalacia (1), angiomatosis (1)	no details	not done	no details	all resection	no details
Fogarasi et al. (2003)	12	child	PS (9), tonic (5), myo (6), ES (1)	MCDs (10), TS (1), abscess (1)	↓ in 7/8	↑ in 1/1	concordant in 11/12	all resection	6/12 SF (50%)
Olavarria and Petronio (2003)[17]	1	infant	GTS	MCDs	↓ in 1/1	not done	concordant	all resection	Engel class II
D'Agostino et al. (2004)[3]	10	child	partial (9), ES (5), myo/drops (2)	CDs (14 HM, 5 MCDs)	↓ in 5/5	↑ in 3/5, ↓ in 1/5	concordant in 9/10	4 disconnect, 6 resection	5/10 SF (50%)
Daniel et al. (2007)[4]	13	adult/ child	partial (12), ES (1), GC (1)	porencephaly (4), MCDs (3), atrophy (3), Sturge-Weber (2), AVM (1)	no details	no details	concordant in 12/13	7 disconnect, 6 resection	12/13 SF (92%)
Novegno et al. (2011)[16]	4	infant	partial (4)	MCDs (4)	no details	no details	concordant in 4/4	4 resection	1/4 SF (25%)
Mohamed et al. (2011)[15]	16	infant/ child	partial (7), ES (10), tonic (7), myo (1)	MCDs (6), angiomatosis (3), cystic encephalomalacia (1), subtle WM signal abnormality (5), subtle sulcus irregularity (1)	↓ in 9/16, not done in 7/16	↑in 6/16, not informative in 3/16, not done in 7/16	concordant in 6/16	14 disconnect, 2 resection	9/16 SF (56%)

AVM: arteriovenous malformation, CD: cortical dysplasia, EEG: electroencephalography, ES: epileptic spasm, GC: generalized clonic, GTS: generalized tonic seizure, HM: hemimegalencephaly, MR: magnetic resonance, myo: myoclonic, PET: positron emission tomography, PS: partial seizure, SF: seizure free, SPECT: single photon emission computed tomography, TS: tuberous sclerosis, WM: white matter.

parietal, and occipital lobes (posterior quadrant) and does not involve the central and frontal areas. In infants, the epileptogenic lesions may be difficult to image because of incomplete myelination.[5] The indication relies on good concordance between the imaging studies (MR imaging, SPECT, and positron emission tomography), EEG, MEG, and clinical and neuropsychological evaluations, which collectively localize the lesion unilaterally to the posterior quadrant. We emphasize this concordance to select patients. In our cases, the preoperative investigations aimed at localizing the epileptogenic zone were concordant and therefore eliminated the need for chronic invasive recording. In addition, it is difficult to perform chronic intracranial electrocorticography on infants. During the operation, the disconnection is tailored to encompass the whole epileptogenic lesion and to avoid the central area, which is likely functional. Our surgical technique is similar to the functional posterior quadrantectomy.[5] We used the postcentral sulcus to define the line of parietal disconnection anterolaterally, which was followed medially to the splenium of the corpus callosum. The identification of the postcentral sulcus in dysplastic hemispheres can be difficult. Prior to the dissection, the primary motor and sensory cortices and postcentral sulcus were identified from a preoperative scrupulous study of the three-dimensional surface rendering from the patient's MR images (Fig. 2) and correlation with intraoperative surface anatomy, based on gyral pattern, superficial arteries, and veins. Electrophysiological localization of central sulcus is also useful using somatosensory evoked potentials or cortical stimulation for mapping of the motor cortex.[4] The surgical accuracy facilitated by such techniques provides the best chance for complete seizure relief.[1,4,15,18]

It is important to note that all three infants treated by our protocols exhibited total control of seizures at the follow-up evaluation (6–12 months after operation). However, the long-term efficacy is yet to be determined. Experience with surgical treatment of such lesions is limited and the results reported in the literature are not uniformly positive (Table 1). In a series of 5 patients with MCDs, 3 patients had satisfactory outcomes; 2 were seizure free, and 1 required monotherapy. The other 2 patients received no permanent benefit from the surgery.[3] In addition, 2 cases had large parieto-occipito-temporal dysplastic lesions and were seizure-free 10 and 17 months after surgery.[20] Of 5 patients with MCDs, 1 patient had Engel's class IIB and 4 patients had Engel's class IIIA outcomes.[11] In a report of 3 infants after surgeries for malformations of cortical development, Engel's class I outcome was obtained in 1 patient.[17] Finally, of 4 infants with MCDs, only 1 patient had Engel's class I and 3 patients had Engel's class II, III, and IV outcomes, respectively.[16]

Our Case 1 and Case 2 presented with delayed development; both 3-month-old infants exhibited DQs of normal 2-month-old infants. Both infants had excellent postoperative recovery and definite catch-up in their development, both motor and cognitive, at postoperative follow-up evaluation 5 months and 12 months, respectively. Previous studies have suggested similar results. For example, in a study of infants treated surgically for catastrophic epilepsy, marked catch-up development was observed in patients with at least 50% reduction in seizures.[19] Previous studies have shown that the noxious effects of catastrophic epilepsy and antiepileptic medications (at high doses) on the developing brain have a deleterious psychomotor impact and usually result in severe epileptic encephalopathy, developmental delay, and mental retardation. In addition, the social implications of a debilitating disease and lost school time due to the encephalopathy are significant negatives.[5] Early surgical intervention in patients who develop intractable epilepsy in infancy or childhood may improve quality of life and possibly cognitive outcomes in the developing child.[6] Furthermore, the need for early surgical intervention after onset of medically refractory epilepsy is supported by studies demonstrating better seizure outcome and improved development in patients with shorter epilepsy duration.[2,8,10] Thus, early surgical intervention is mandatory in cases of intractable epilepsy with extensive MCDs in infants.

All 3 cases reported here had excellent postoperative recovery and no complications have been detected to date. However, the long-term complications including an inevitable homonymous visual field deficit, if any, are yet to be determined. Epilepsy surgery in infants poses a higher risk of perioperative complications. In a series of 12 infants who underwent surgery for catastrophic epilepsy, 1 death and 2 postoperative complications (subdural hematoma and loculated temporal horn) occurred.[20] Two of 13 patients under 3 years of age died (operative mortality of 6%).[7] The disconnective technique is the logical evolution of the concept of an anatomically subtotal, but functionally complete resection in subhemispheric dysplasias. This procedure minimizes the size of the resection cavity and consequently reduces perioperative morbidity, in addition to preventing hydrocephalus.[5] As the dysplastic cortex left behind is completely disconnected, seizure outcomes are identical to those for multilobar resection.[18] Our cases show that intractable epilepsy was alleviated with a more limited resection using the disconnective technique.

Early application of the disconnective technique for extensive MCDs can result in good seizure control and developmental outcomes with little perioperative morbidity at follow-up within a year after surgery. Long-term follow-up evaluation will be required to verify the efficacy of this surgical technique. We believe that disconnective techniques will decrease the potential of long-term complications associated with large brain excisions.

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Conflicts of Interest Disclosure

The authors have no conflicts of interest to disclose. All authors who are members of The Japan Neurosurgical So-

ciety (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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Address reprint requests to: Akio Takahashi, MD, PhD, Department of Neurosurgery, National Center Hospital of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan.
e-mail: akiotaka@ncnp.go.jp

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Original article

Surgical management of cortical dysplasia in infancy and early childhood ☆

Taisuke Otsuki [a,*], Ryoko Honda [b], Akio Takahashi [a], Takanobu Kaido [a], Yu Kaneko [a], Tetsuji Nakai [c], Yuko Saito [d], Masayuki Itoh [e], Eiji Nakagawa [b], Kenji Sugai [b], Masayuki Sasaki [b]

[a] *Department of Neurosurgery, Epilepsy Center, National Center of Neurology and Psychiatry, Tokyo, Japan*
[b] *Department of Child Neurology, Epilepsy Center, National Center of Neurology and Psychiatry, Tokyo, Japan*
[c] *Department of Anesthesiology, Epilepsy Center, National Center of Neurology and Psychiatry, Tokyo, Japan*
[d] *Department of Pathology and Laboratory Medicine, Epilepsy Center, National Center of Neurology and Psychiatry, Tokyo, Japan*
[e] *Department of Mental Retardation and Birth Defect Research, Epilepsy Center, National Center of Neurology and Psychiatry, Tokyo, Japan*

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Abstract

Purpose: To describe operative procedures, seizure control and complications of surgery for cortical dysplasia (CD) causing intractable epilepsy in infancy and early childhood. *Methods:* Fifty-six consecutive children (less than 6 years old) underwent resective epilepsy surgery for CD from December 2000 to August 2011. Age at surgery ranged from 2 to 69 months (mean 23 months) and the follow-up was from 1 to 11 years (mean 4 years 4 months). *Results:* Half of the children underwent surgery during infancy at an age less than 10 months, and the majority (80%) of these infants needed extensive surgical procedures, such as hemispherotomy and multi-lobar disconnection. Seizure free (ILAE class 1) outcome was obtained in 66% of the cases (class 1a; 55%): 85% with focal resection ($n = 13$), 50% with lobar resection ($n = 18$), 71% with multilobar disconnection ($n = 7$) and 67% with hemispherotomy ($n = 18$). Peri-ventricular and insular structures were resected in 23% of focal and 61% of lobar resections. Repeated surgery was performed in 9 children and 5 (56%) became seizure free. Histological subtypes included hemimegalencephaly (16 patients), polymicrogyria (5 patients), and FCD type I (6 patients), type IIA (19 patients), type IIB (10 patients). Polymicrogyria had the worst seizure outcome compared to other pathologies. Surgical complications included 1 post-operative hydrocephalus, 1 chronic subdural hematoma, 2 intracranial cysts, and 1 case of meningitis. No mortality or severe morbidities occurred. *Conclusions:* Early surgical intervention in children with CD and intractable seizures in infancy and early childhood can yield favorable seizure outcome without mortality or severe morbidities although younger children often need extensive surgical procedures.

Keywords: Epilepsy surgery; Infant; Focal cortical dysplasia; Hemimegalencephaly; Polymicrogyria; Hemispherotomy; Multilobar disconnection; Seizure outcome

1. Introduction

Frequent epileptic seizures in infants cause severe epileptic encephalopathy associated with progressive developmental delay. Cortical dysplasia (CD), or malformations in cortical development, is increasingly recognized as a cause of intractable epilepsy in infancy [1,2].

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* Corresponding author. Address: Department of Neurosurgery, Epilepsy Center, National Center of Neurology and Psychiatry, Ogawahigashi-4-1-1, Kodaira, Tokyo 187-8551, Japan. Tel.: +81 42 341 2711; fax: +81 42 346 1793.
E-mail address: otsukit@ncnp.go.jp (T. Otsuki).

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The CD spectrum covers distinct focal cortical lesions to extensive hemispheric pathology and is classified histologically as focal cortical dysplasia (FCD), heterotopia, polymicrogyria (PMG), schizencephaly, lissencephaly, and hemimegalencephaly (HMC) [3,4]. Among these, FCD and HMC are the 2 most frequent types in reported surgical series thus far.

Histologically, FCD is subclassified as FCD type I, type IIA, and type IIB [4]. FCD type I presents as neocortical dyslamination, ectopic white matter neurons, and/or giant neurons. FCD type II is characterized by the additional presence of dysmorphic neurons (type IIA) and balloon cells (type IIB). Magnetic resonance imaging (MRI) of FCD type I is frequently negative, but may show slight signal changes in subcortical white matter [5]. FCD type II MRI typically shows thickened cortical ribbon, blurred gray-white junctions, cortical and subcortical signal changes, and transmantle sign. HMC demonstrates an enlarged unilateral hemisphere with gross anatomical malformations in cortical and subcortical structures associated with variety of histopathological abnormalities identified in other forms of CD [6].

A contemporary series of resective surgery for CD reports that more than 60% of patients are seizure free, with higher rates for complete removal of the lesion [7–10]. Morbidity (<3%) and mortality (0.2%) are low for patients with CD undergoing epilepsy neurosurgery. Moreover, patients operated on at younger ages reportedly show larger increases in developmental quotient (DQ) after surgery [1,11–12]. Attention, therefore, is now focused on early surgery to avoid the negative influence of frequent intractable seizures on the immature brain causing epileptic encephalopathy in early life.

However, early epilepsy surgery in infancy was reported to have high intraoperative complications and mortality rate [13,14]. Duchowny et al. [13] reported that the surgical mortality was 6% in their series of 31 infants who were under 3 years of age. Basheer et al. [14] also reported that age (<2 years old), weight (<11 kg), and hemidecortication were risk factors for transfusion and post-operative hydrocephalus developed in 13% of the 24 children in their series.

Recently, introduction of less-invasive disconnective surgical procedures such as hemispherotomy [15–16] and posterior multilobar disconnection [18,19], which totally disconnect epileptic cortices from the rest of the brain but spare major vasculature, have been facilitating safe and reliable epilepsy surgery in children. Although the patient number is still small, recent literature reported favorable outcomes in radical epilepsy surgery for CD in early infancy [8,20,21]. However, more data are needed to clarify the indication of surgical procedures, timing, outcome, and risk of epilepsy surgery for CD presenting in infancy and early childhood.

2. Patients and methods

2.1. Subjects

We retrospectively studied 56 consecutive children (33 male patients, 23 female patients) who had medically refractory epilepsy with CD and underwent resective surgery at less than 6 years of age at the National Center of Neurology and Psychiatry from December 2000 to August 2011. Patients with tuberous sclerosis, dysplastic tumors, and encephalomalacia were excluded from the study.

Age at seizure onset ranged from birth to 27 months (median: 1 months, mean: 4 months) and age at surgery ranged from 2 to 69 months (median: 10 months, mean: 23 months) (Fig. 1). Twenty patients were operated within 6 months of birth. The follow-up period from the last surgery ranged from 12 months to 11 years (median: 4 years, mean: 4 years 4 months). All patients had drug-resistant multiple daily seizures, such as epileptic spasms, tonic seizures, or epilepsia partialis continua. No patient had a history of perinatal or postnatal systemic complications suggesting brain injury. In 4 cases, resective surgery was indicated at 1 month to 2 years (mean: 16 months) after callosotomy, which had revealed lateralized epileptogenicity.

2.2. Pre-surgical evaluation

All patients underwent comprehensive pre-surgical evaluations including electroencephalography (EEG), 1.5- or 3.0- Tesla MRI, ictal video-EEG monitoring, fluorodeoxyglucose-positron emission tomography (FDG-PET), magnetoencephalography (MEG), and developmental assessments. All, but 5, patients demonstrated MRI abnormalities, which varied from a subtle focal cortical or subcortical change to hemispheric structural abnormality. Subtraction ictal 99mTc-ethyl cysteinate dimer single-photon emission tomography (SPECT) coregistered to MRI (SISCOM) was indicated in 27 cases. Intracranial EEG monitoring with subdural and depth electrodes was performed under sedation and intensive care over 3 days in 7 patients (3 frontal, 2 temporal, 1 central, and 1 parietal lobe) over 35 months of age.

2.3. Peri-operative management

Central venous catheterization for blood transfusion was mandatory for infants less than 6 months. Blood transfusion, packed red blood cells, and fresh frozen plasma (FFP) was used during surgery as required. FFP of 10 ml/kg was routinely transfused for small infants who were less than 7 kg perioperatively for hemispheric surgeries, for which total blood loss was 150–250 ml and total time was 5–6 h.

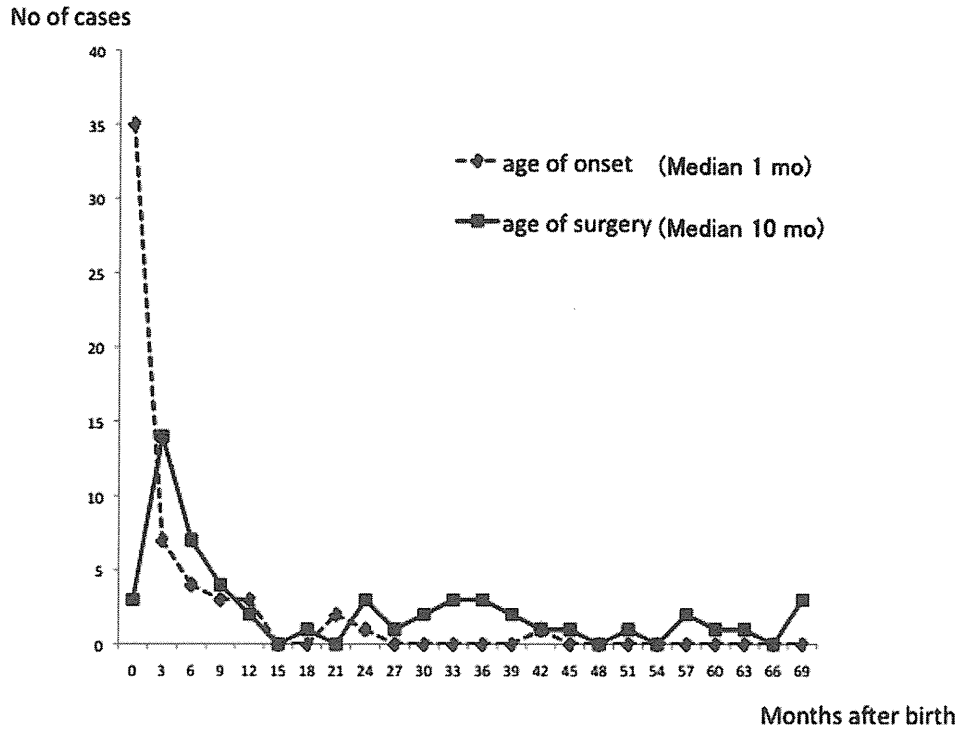

Fig. 1. Age of onset and age of surgery (months) in 56 children.

2.4. Method for assessing outcomes

Seizure outcomes were assessed using the International League Against Epilepsy (ILAE) classification [22].

2.5. Statistical analyses

Fisher's exact test was used to compare surgical outcome (seizure free vs. not free) to surgical procedures (focal resection vs. others) and histological subtypes (PMG vs. others). We considered $P < 0.05$ as statistically significant.

3. Results

3.1. Surgical procedures

The surgical procedure used and age at surgery for the 56 children is shown in Fig. 2. Twenty-eight patients (50%) were operated on during infancy (<12 months). Extensive surgical procedures, including hemispherotomy and multilobar disconnection, were more often indicated in infants than in older children.

Focal resection (Fig. 3), less than 4 cm at the largest diameter, was indicated in 13 patients. The resection area included all MRI-visible lesions, together with MRI non-visible areas, demonstrating the congruency of ictal hyper-perfusion, MEG dipole clustering, and FDG-PET hypometabolism. In 3 of these patients (23%), periventricular and insular regions, which were continuous to the cortical lesion, were also resected. Lobar resection (Fig. 4) was indicated in 18 patients. Periventricular and insular structures were also resected in 11 cases (61%), all of which were added in extensive frontal lobectomy. Multilobar disconnection (Fig. 5) was indicated in 7 patients; 2 to the anterior and 5 to the posterior half of the hemisphere. Hemispherotomy (Fig. 6) was indicated in 18 patients, 17 by vertical and 1 by horizontal approach.

3.2. Seizure outcome

Seizure outcome at the last follow-up was ILAE class 1 in 37 cases (66%); there were no class 2 cases, two class 3 cases (4%), five class 4 cases (9%), and twelve class 5 cases (21%) (Fig. 7). Thirty-one children (55%) were completely seizure free after surgery (class 1a). Upon comparison of the type of surgical procedures, class 1 outcome was obtained in 85% of patients with focal resection, 50% of patients with lobar resection, 71% of patients with multilobar disconnection, and 67% of patients with hemispherotomy. Although the differences were not statistically significant, better seizure outcome was obtained after focal resection compared to the other procedures ($0.05 < P < 0.1$).

3.3. Histopathological diagnoses

Histological subtypes included HMC (16 patients), PMG (5 patients), and FCD type I (6 patients), IIA (19 patients), and IIB (10 patients). The histopathology,

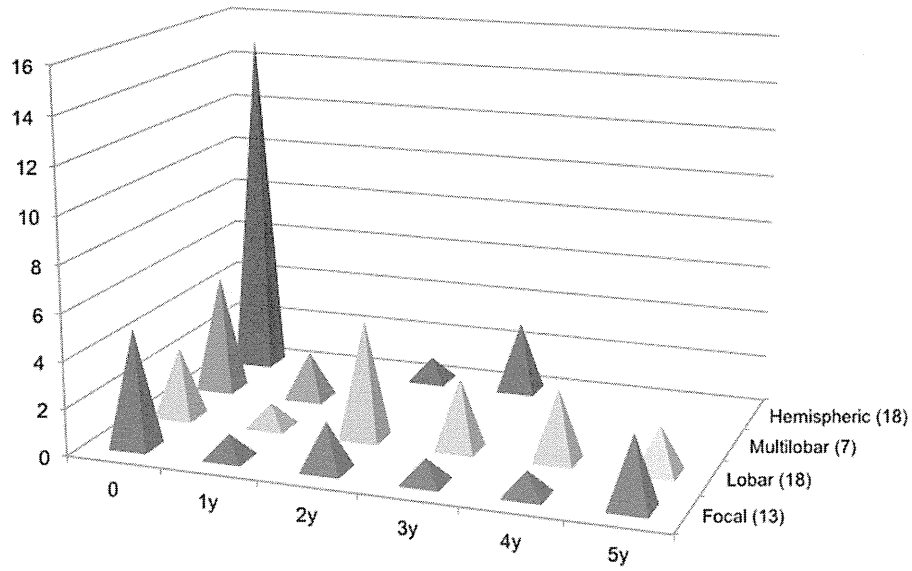

Fig. 2. Surgical procedure and age at surgery. Focal: focal resection; lobar: lobar resection/disconnection; multilobar: multilobar disconnection; hemispheric: hemispherotomy. Parentheses indicate the number of patients.

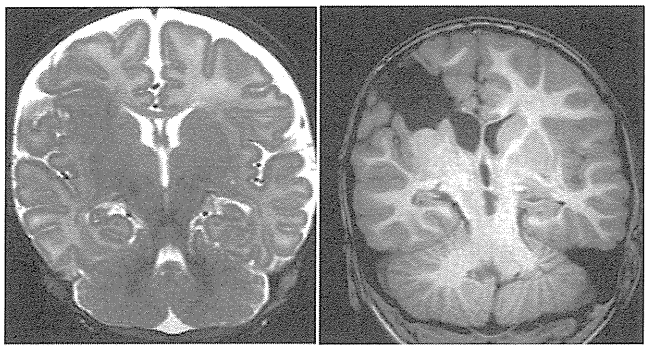

Fig. 3. Focal resection indicated for a bottom of sulcus FCD type in the frontal lobe. All MRI-visible lesions that invaded to the periventricular white matter and parts of the insular cortex and striatum were completely resected. (Left) pre-op, and (right) post-op.

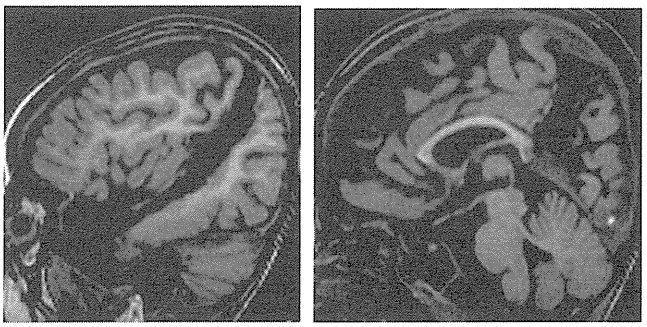

Fig. 5. Multilobar (posterior) disconnection indicated for temporo–occipito–parietal CD. The posterior half of the hemisphere was disconnected from the postcentral sulcus.

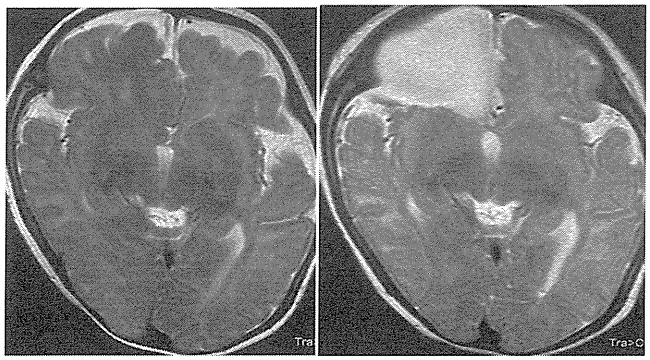

Fig. 4. Lobar resection indicated for a frontal lobe CD. All MRI-visible lesions in front of the nucleus accumbens at the line connecting the bottom of peri-insular sulcus, limen insulae, and subcallosal area were completely resected. Left panel: pre-op. Right panel: post-op.

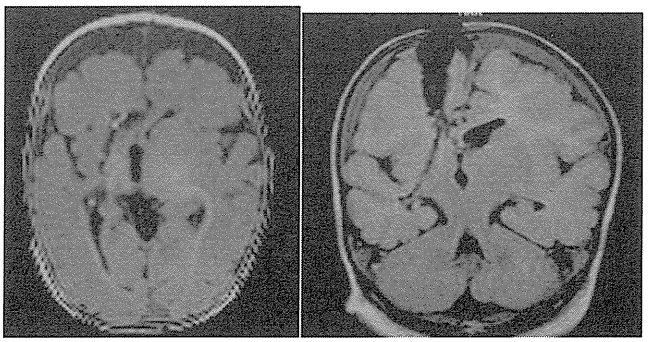

Fig. 6. Vertical hemispherotomy (Delalande's approach) indicated for a case of HMC. Cortical and subcortical structures surrounding the striatum and thalamus of the right hemisphere were totally disconnected. Left panel: axial view. Right panel: coronal view.