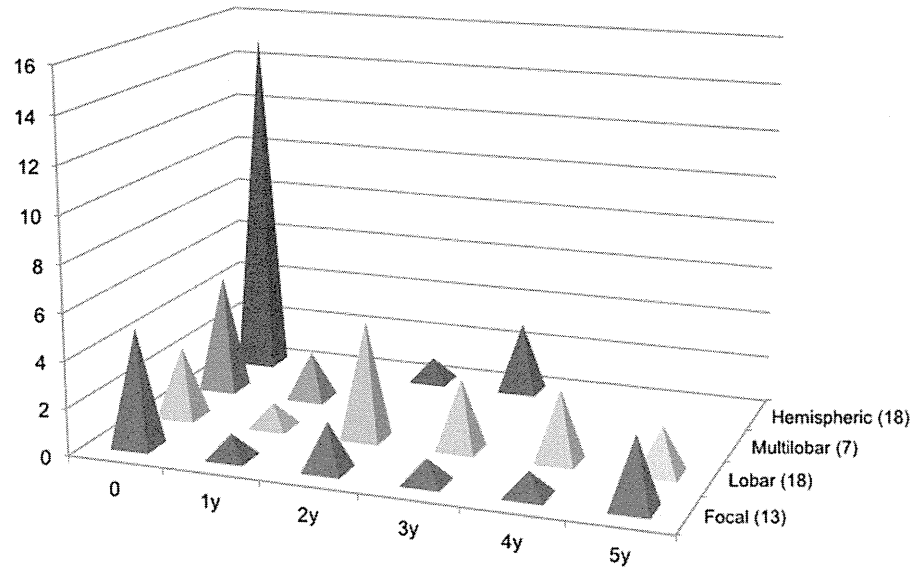

Fig. 2. Surgical procedure and age at surgery. Focal: focal resection; lobar: lobar resection/disconnection; multilobar: multilobar disconnection; hemispheric: hemispherotomy. Parentheses indicate the number of patients.

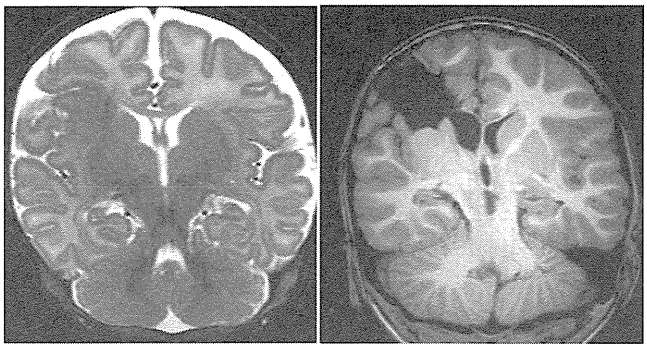

Fig. 3. Focal resection indicated for a bottom of sulcus FCD type in the frontal lobe. All MRI-visible lesions that invaded to the periventricular white matter and parts of the insular cortex and striatum were completely resected. (Left) pre-op, and (right) post-op.

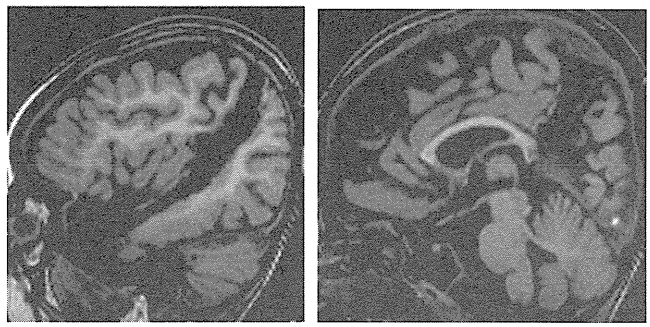

Fig. 5. Multilobar (posterior) disconnection indicated for temporo–occipito–parietal CD. The posterior half of the hemisphere was disconnected from the postcentral sulcus.

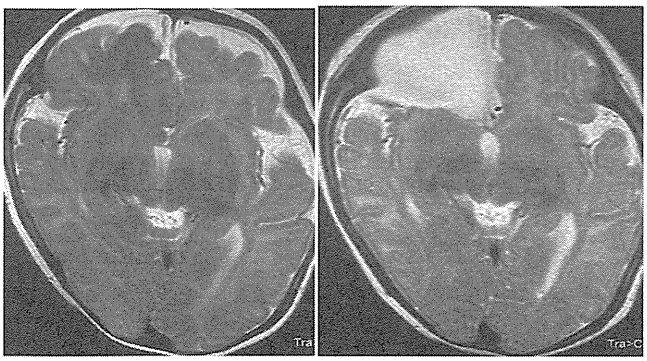

Fig. 4. Lobar resection indicated for a frontal lobe CD. All MRI-visible lesions in front of the nucleus accumbens at the line connecting the bottom of peri-insular sulcus, limen insulae, and subcallosal area were completely resected. Left panel: pre-op. Right panel: post-op.

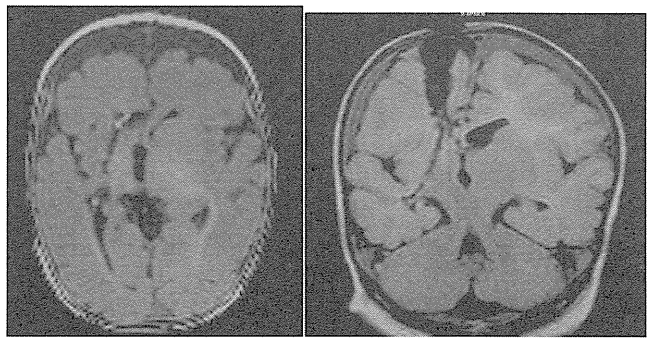

Fig. 6. Vertical hemispherotomy (Delalande's approach) indicated for a case of HMC. Cortical and subcortical structures surrounding the striatum and thalamus of the right hemisphere were totally disconnected. Left panel: axial view. Right panel: coronal view.

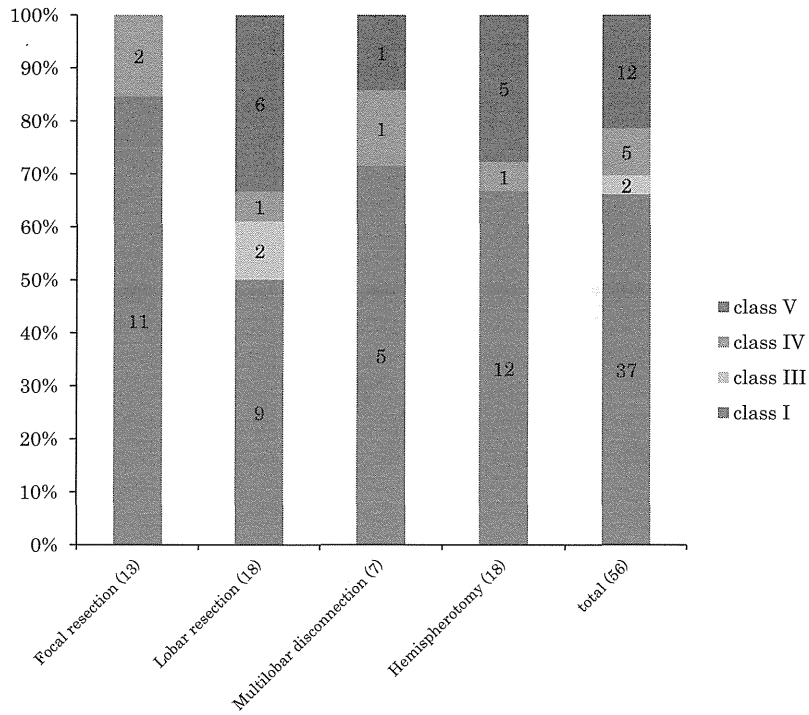

Fig. 7. Surgical procedure and seizure outcome (ILAE classification). Parentheses indicate the number of patients.

Table 1
Histopathology, surgical procedures and seizure outcome of 56 patients. Parentheses indicate number of seizure free (class I) patients.

Surgery CD type	Focal resection	Lobar resection	Multilobar disconnection	Hemispherotomy	Total	Class I (%)
HMC				16 (11)	16 (11)	69%
PMG		2 (0)	2 (1)	1 (0)	5 (1)	20%*
FCD type I	2 (2)	4 (1)			6 (3)	50%
FCD type IIA	6 (4)	7 (5)	5 (4)	1 (1)	19 (14)	74%
FCD type IIB	5 (5)	5 (3)			10 (8)	80%
Total	13 (11)	18 (9)	7 (5)	18 (12)	56 (37)	66%
Class I (%)	85%	50%	71%	67%		

HMC: hemimegalencephaly, PMG: polymicrogyria, FCD: focal cortical dysplasia.
* $P < 0.05$.

surgical procedure, and seizure outcome of the patients are listed in Table 1. Class 1 outcome was obtained in 69% of patients with HMC, 20% of patients with PMG, 50% of patients with FCD type I, 74% of patients with FCD type IIA, and 80% of patients with FCD type IIB. There were no statistical differences in seizure outcome among CD histological subtypes except PMG ($P < 0.05$), in which 4 children remained in class 5 even though 2 underwent repeated surgery and 1 patient underwent hemispherotomy.

3.4. Repeated surgery

Because of recurrent seizures, repeated surgery was indicated in 9 cases (1 patient received 3 surgeries) at 1–20 months (mean: 9 months) after the initial surgery. The repeated surgeries included 2 focal, 6 lobar, and 1 multilobar procedures. Seizure freedom was finally obtained in 5 children (56%; all class 1a). In all cases but 1, additional resection at the insular and periventricular structures was indicated.

3.5. Surgical complications

Surgical complications were experienced in 5 cases (9%); these included 1 post-operative hydrocephalus, 1 chronic subdural hematoma, 2 intracranial cyst formation at resected cavity, and 1 transient meningitis that were successfully managed without sequel by ventricular peritoneal shunt, burr hole irrigation, cyst wall resection, and antibiotics administration, respectively. No mortality or severe morbidity occurred.

4. Discussion

The present report demonstrates that 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. Post-operatively, ILAE class 1 (seizure free) outcome was obtained in 66% of the cases, and class 1a (completely seizure free since the surgery) outcome was observed in 55% of the cases in a mean follow-up of 4 years.

Half of the children underwent surgery were 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. Post-operative seizure outcome did not differ significantly with the type of surgery although it was slightly better for focal resection: 85% with focal resection, 50% with lobar resection, 71% with multilobar disconnection, and 67% with hemispherotomy. These data may indicate that careful and meticulous pre-surgical evaluations are valuable to localize epileptogenicity and to pursue minimum tissue removal in infants.

However, pre-surgical evaluations for infants with intractable seizures are challenging, particularly when epileptic encephalopathy is associated [23]. This is because interictal scalp EEG frequently shows bilateral abnormalities, the localizing value of ictal semiology in infant is limited, and MRI only demonstrates tissues with severe histological abnormalities. Therefore, to define a focal epileptogenicity, the role of additional diagnostic modalities, such as FDG-PET, ictal SPECT, MEG, and intra-cranial EEG monitoring have been stressed [24–29].

Our strategy for resective epilepsy surgery in infancy was principally based on multimodal neuroimaging, that is, co-registering all the imaging data obtained and checking congruency of MRI findings to FDG-PET abnormalities, ictal hyper-perfusion, and MEG dipole clustering. The resection plan basically included all MRI-visible and non-visible pathologies congruent to such diagnostic modalities, which often included not only cortical but also subcortical structures [30,31].

We recently reported a series of 8 children with extensive frontal lobe CD, in which pre-surgical functional neuroimaging studies showed ictal hyper-perfusion, reduced iomazenil uptake, and/or spike dipole clustering in subcortical structures surrounding the anterior horn of the lateral ventricle [32]. In all patients, seizure freedom was obtained after resection of the peri-ventricular white matter and part of the striatum, where histological evaluation revealed dysplastic neurons in some cases.

Epileptogenicity in subcortical brain structures has not been well elucidated. However, the data indicate that hemispherotomy, either by a horizontal or vertical approach, achieves complete disconnection of all cortical and subcortical structures surrounding the striatum and thalamus, which includes the insular cortex, the limen insulae, and the subcallosal area [15–17,33]. Incomplete removal of these structures is reported to cause surgical failure [34,35]. Moreover, some authors had even mentioned the role of resection of a part of the basal ganglia and thalamus to prevent recurrent seizures [33].

It is considered rational, therefore, to remove the CD located at the structures covering the striatum and thalamus in order to obtain favorable seizure outcome. Anatomically, these structures include not only the insular cortex but also the bottom of deep cortical sulci surrounding the striatum and thalamus, such as the vertical ramus of the Sylvian fissure and the circular insular sulcus, which locate close to the periventricular white matter. In our series, periventricular and insular regions, which were continuous to the cortical pathologies, were also removed in 23% of focal resection and 61% of lobar resection, which may have yielded our comparatively good seizure outcome.

Histological subtypes of CD may influence seizure outcome. CD, in general, is extremely variable and usually treatable by surgery when it is focal or within one hemisphere [4,36–38]. Although FCD is commonly confined to a single hemisphere, PMG, lissencephaly, and pachygyria often involve both cerebral hemispheres [4,36], in which the pathophysiological bases are heterogeneous and include genetic causes [39]. HMC is also known to associate with dysplastic contralateral abnormalities [6], which have been reported as a negative factor for post-surgical seizure and developmental outcome [38,40,41].

Subtypes of FCD may also affect surgical outcome [10,42]. It is reported that the seizure outcome of resective surgery in young children with FCD type I was not as good as that in children with to FCD type II [5,43]. On average, post-operative seizure freedom (Engel class I) was reported in 47% (range 21–67%) of patients with FCD type I and 76% (range 60–100%) of patients with FCD type IIB [4,5,44–48]. However, FCD type IIA is less well characterized and only a few studies have addressed it thus far [4,46,49]. Although our sample size was small, we did not obtain statistically different seizure outcomes (class 1) among CD subtypes except in PMG (HMC 69%, PMG 20%, FCD type I 50%, FCD type IIA 74%, and FCD type IIB 80%). More studies are needed to clarify the difference in the nature of epileptogenicity among histological subtypes of FCD.

5. 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.

Acknowledgements

The authors are grateful for the contributions of Prof. Nobutaka Arai, Department of Clinical Neuropathology, Tokyo Metropolitan Institute for Neuroscience, Tokyo, and Prof. Akiyoshi Kakita, Department of Pathological Neuroscience, Brain Research Institute, University of Niigata, Niigata, for neuropathological diagnoses of all specimens obtained from our epilepsy surgery program.

None of the authors has any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with their guidelines.

Part of this work has been presented at the International Symposium on Surgery for Catastrophic Epilepsy in Infants (ISCE), the 14th Annual Meeting of ISS, Tokyo, February 18–19, 2012. This study was supported in part by a Health Labor Sciences Research Grant from the Ministry of Health Labor and Welfare of Japan.

References

[1] Wyllie E, Comair YG, Kotagal P, Raja S, Ruggieri P. Epilepsy surgery in infants. Epilepsia 1996;37:625–37.
[2] Lortie A, Plouin P, Chiron C, Delalande O, Dulac O. Characteristics of epilepsy in focal cortical dysplasia in infancy. Epilepsy Res 2002;51:133–45.
[3] Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology 2005;65:1873–87.
[4] Blümcke I, Vinters HV, Armstrong D, Aronica E, Thom M, Spreafico R. Malformations of cortical development and epilepsies: neuropathological findings with emphasis on focal cortical dysplasia. Epileptic Disord 2009;11:181–93.
[5] Krsek P, Pieper T, Karlmeier A, Hildebrandt M, Kolodziejczyk D, Winkler P, et al. Different presurgical characteristics and seizure outcomes in children with focal cortical dysplasia type I or II. Epilepsia 2009;50:125–37.
[6] De Rosa MJ, Secor DL, Barsom M, Fisher RS, Vinters HV. Neuropathologic findings in surgically treated hemimegalencephaly: immunohistochemical, morphometric, and ultrastructural study. Acta Neuropathol 1992;84:250–60.
[7] Hader WJ, Mackay M, Otsubo H, Chitoku S, Weiss S, Becker L, et al. Cortical dysplastic lesions in children with intractable epilepsy: role of complete resection. J Neurosurg Pediatr 2004;100(Suppl. 2):110–7.
[8] Mathern GW. Challenges in the surgical treatment of epilepsy patients with cortical dysplasia. Epilepsia 2009;50(Suppl. 9):45–50.
[9] Chang EF, Wang DD, Barkovich AJ, Tihan T, Auguste KI, Sullivan JE, et al. Predictors of seizure freedom after surgery for malformations of cortical development. Ann Neurol 2011;70:151–62.
[10] Rowland NC, Englot DJ, Cage TA, Sughrue ME, Barbaro NM, Chang EF. A meta-analysis of predictors of seizure freedom in the surgical management of focal cortical dysplasia. J Neurosurg 2012;116:1035–41.
[11] Asarnow RF, LoPresti C, Guthrie D, Elliott T, Cynn V, Shields WD, et al. Developmental outcomes in children receiving resection surgery for medically intractable infantile spasms. Dev Med Child Neurol 1997;39:430–40.
[12] Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E. Developmental outcome after epilepsy surgery in infancy. Pediatrics 2007;119:930–5.
[13] Duchowny M, Jayakar P, Resnick T, Harvey AS, Alvarez L, Dean P, et al. Epilepsy surgery in the first three years of life. Epilepsia 1998;39:737–43.
[14] Basheer SN, Connolly MB, Lautzenhiser A, Sherman EM, Hendson G, Steinbok P. Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function. Epilepsia 2007;48:133–40.
[15] Villemure JG, Mascott CR. Peri-insular hemispherotomy: surgical principles and anatomy. Neurosurgery 1995;37:975–81.
[16] Schramm J, Kral T, Clusmann H. Transsylvian keyhole functional hemispherectomy. Neurosurgery 2001;49:891–900.
[17] Delalande O, Bulteau C, Dellatolas G, Fohlen M, Jalin C, Buret V, et al. Vertical parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a population of 83 children. Neurosurgery 2007;60(Suppl. 1,2) ONS19–32.
[18] Daniel RT, Meagher-Villemure K, Farmer JP, Andermann F, Villemure JG. Posterior quadrantic epilepsy surgery: technical variants, surgical anatomy, and case series. Epilepsia 2007;48:1429–37.
[19] Liang Q, Otsuki T, Takahashi A, Enokizono T, Kaido T, Kaneko Y, et al. Posterior disconnection in early infancy to treat intractable epilepsy with multilobar cortical dysplasia: report of three cases. Neurol Med Chirur 2013;53:47–52.
[20] Lettori D, Battaglia D, Sacco A, Veredice C, Chieffo D, Massimi L, et al. Early hemispherectomy in catastrophic epilepsy: a neurocognitive and epileptic long-term follow-up. Seizure 2008;17:49–63.
[21] Gowda S, Salazar F, Bingaman WE, Kotagal P, Lachhwani DL, Gupta A, et al. Surgery for catastrophic epilepsy in infants 6 months of age and younger. J Neurosurg Pediatr 2010;5:603–7.
[22] Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, et al. Commission on Neurosurgery of the International League Against Epilepsy (ILAE). ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. Epilepsia 2001;42:282–6.
[23] Wyllie E, Lachhwani DK, Gupta A, Chirla A, Cosmo G, Worley S, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. Neurology 2007;24(69):389–97.
[24] Sisodiya SM. Surgery for focal cortical dysplasia. Brain 2004;127:2383–4.
[25] Salamon N, Kung J, Shaw SJ, Koo J, Koh S, Wu JY, et al. FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. Neurology 2008;71:1594–601.
[26] Obeid M, Wyllie E, Rahi AC, Mikati MA. Approach to pediatric epilepsy surgery: state of the art, part I: general principles and presurgical workup. Eur J Paediatr Neurol 2009;13:102–14.
[27] Chassoux F, Rodrigo S, Semah F, Beuvon F, Landre E, Devaux B, et al. FDG-PET improves surgical outcome in negative MRI Taylor-type focal cortical dysplasias. Neurology 2010;75:2168–75.
[28] Kim YH, Kang HC, Kim DS, Kim SH, Shim KW, Kim HD, et al. Neuroimaging in identifying focal cortical dysplasia and prognostic factors in pediatric and adolescent epilepsy surgery. Epilepsia 2011;52:722–7.
[29] Seo JH, Holland K, Rose D, Rozhkov L, Fujiwara H, Byars A, et al. Multimodality imaging in the surgical treatment of children with nonlesional epilepsy. Neurology 2011;76:41–8.
[30] Nakayama T, Otsuki T, Kaneko Y, Nakama H, Kaido T, Otsubo H, et al. Repeat magnetoencephalography and surgeries to eliminate atonic seizures of non-lesional frontal lobe epilepsy. Epilepsy Res 2009;84:263–7.
[31] Kaido T, Otsuki T, Kaneko Y, Takahashi A, Kakita A, Takahashi H, et al. Anterior striatum with dysmorphic neurons

associated with the epileptogenesis of focal cortical dysplasia. Seizure 2010;19:256–9.
[32] Kaido T, Otsuki T, Kakita A, Sugai K, Saito Y, Sakakibara T, et al. Novel pathological abnormalities of deep brain structures including dysplastic neurons in anterior striatum associated with focal cortical dysplasia in epilepsy. J Neurosurg Pediatr 2012;10:217–25.
[33] Cook SW, Nguyen ST, Hu B, Yudovin S, Shields WD, Vinters HV, et al. Cerebral hemispherectomy in pediatric patients with epilepsy: comparison of three techniques by pathological substrate in 115 patients. J Neurosurg Pediatr 2004;100(Suppl.):125–41.
[34] González-Martínez JA, Gupta A, Kotagal P, Lachhwani D, Wyllie E, Lüders HO, et al. Hemispherectomy for catastrophic epilepsy in infants. Epilepsia 2005;46:1518–25.
[35] Cats EA, Kho KH, Van Nieuwenhuizen O, Van Veelen CW, Gosselaar PH, Van Rijen PC. Seizure freedom after functional hemispherectomy and a possible role for the insular cortex: the Dutch experience. J Neurosurg 2007;107(Suppl. 4):275–80.
[36] Fauser S, Sisodiya SM, Martinian L, Thom M, Gumbinger C, Huppertz HJ, et al. Multi-focal occurrence of cortical dysplasia in epilepsy patients. Brain 2009;132:2079–90.
[37] Hallbook T, Ruggieri P, Adina C, Lachhwani DK, Gupta A, Kotagal P, et al. Contralateral MRI abnormalities in candidates for hemispherectomy for refractory epilepsy. Epilepsia 2010;51:556–63.
[38] Kometani H, Sugai K, Saito Y, Nakagawa E, Sakuma H, Komaki H, et al. Postnatal evolution of cortical malformation in the "non-affected" hemisphere of hemimegalencephaly. Brain Dev 2010;32:412–6.
[39] Quelin C, Saillour Y, Poirier K, Roubertie A, Boddaert N, Desguerre I, et al. Focal polymicrogyria are associated with submicroscopic chromosomal rearrangements detected by CGH microarray analysis. Eur J Med Genet 2012;55:527–30.
[40] Boshuisen K, van Schooneveld MM, Leijten FS, de Kort GA, van Rijen PC, Gosselaar PH, et al. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. Neurology 2010;75:1623–30.
[41] Salamon N, Andres M, Chute DJ, Nguyen ST, Chang JW, Huynh MN, et al. Contralateral hemimicrencephaly and clinical-pathological correlations in children with hemimegalencephaly. Brain 2006;129:352–65.
[42] Lerner JT, Salamon N, Hauptman JS, Velasco TR, Hemb M, Wu JY, et al. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. Epilepsia 2009;50:1310–36.
[43] Hildebrandt M, Pieper T, Winkler P, Kolodziejczyk D, Holthausen H, Blümcke I. Neuropathological spectrum of cortical dysplasia in children with severe focal epilepsies. Acta Neuropathol 2005;110:1–11.
[44] Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, et al. Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain 2002;125:1719–32.
[45] Fauser S, Schulze-Bonhage A, Honegger J, Carmona H, Huppertz HJ, Pantazis G, et al. Focal cortical dysplasia: surgical outcome in 67patients in relation to histological subtypes and dual pathology. Brain 2004;127:2406–18.
[46] Krsek P, Maton B, Korman B, Pacheco-Jacome E, Jayakar P, Dunoyer C, et al. Different features of histopathological subtypes cortical dysplasia. Ann Neurol 2008;63:758–69.
[47] Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry 1971;34:369–87.
[48] Urbach H, Scheffler B, Heinrichsmeier T, von Oertzen J, Kral T, Wellmer J, et al. Focal cortical dysplasia of Taylor's balloon cell type: a clinicopathological entity with characteristic neuroimaging and histopathological features, and favorable postsurgical outcome. Epilepsia 2002;43:33–40.
[49] Boonyapisit K, Najm I, Klem G, Ying Z, Burrier C, LaPresto E, et al. Epileptogenicity of focal malformations due to abnormal cortical development: direct electrocorticographic-histopathologic correlations. Epilepsia 2003;44:69–76.

ELSEVIER

Brain & Development 35 (2013) 742–747

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

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*

Received 9 November 2012; received in revised form 9 May 2013; accepted 11 May 2013

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,

☆ Part of this work has been presented at the International Symposium on Surgery for Catastrophic Epilepsy in Infants (ISCE), the Fourteenth Annual Meeting of ISS, Tokyo, February 18-19, 2012.

* 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).

0387-7604/$ - see front matter © 2013 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.braindev.2013.05.004

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

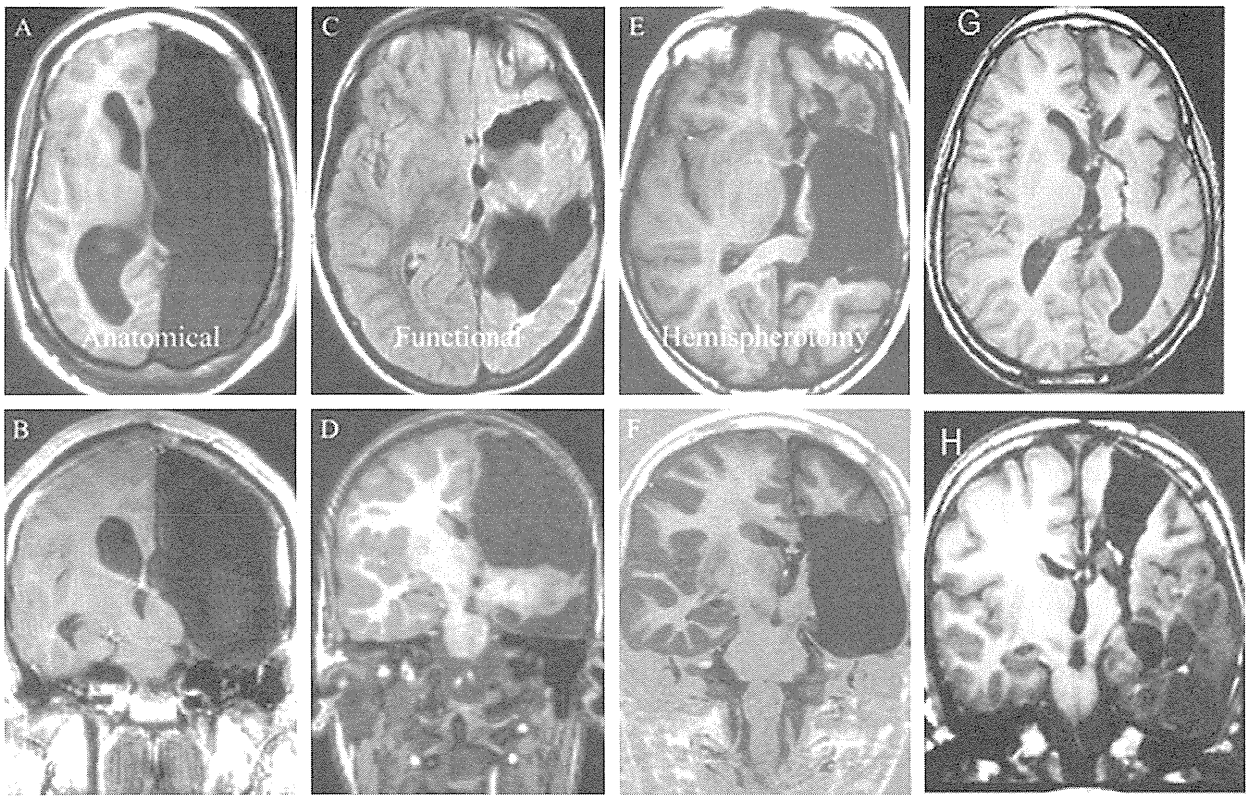

Fig. 1. Axial (upper) and coronal (lower) MRI scans demonstrating the main surgical procedure for hemispheric disconnexion; (A–F) belong to Cook et al. (2004), (G) and (H) belong to Delalande et al. (2007). (A and B): Anatomical hemispherectomy produced by removal of the entire hemisphere including most 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.

Acknowledgements

We thank Pr Olivier DULAC for reviewing the manuscript. The authors have no conflicts of interest to declare.

References

[1] Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006;47:952–9.

[2] Vining EPG, Freeman JM, Pillas DJ, Uematsu S, Carson BS, Brandt J, et al. Why would you remove half a brain? The outcome of 58 children after hemispherectomy-the Johns Hopkins experience: 1968–1996. Pediatrics 1997;100:163–71.

[3] Harvey AS, Cross JH, Shinnar S, Mathern GW. Defining the spectrum of international practice in pediatric epilepsy surgery patients. Epilepsia 2008;49:146–55.
[4] Vigevano F, Bertini E, Boldrini R, Bosman C, Claps D, di Capua M, et al. Hemimegalencephaly and intractable epilepsy: benefits of hemispherectomy. Epilepsia 1989;30:833–43.
[5] Chen HL, Wang PJ, Tu YK, Tseng SH, Yao YT, Young C, et al. Hemimegalencephaly treated by hemispherectomy: report of two cases. J Formos Med Assoc 1994;93:961–6.
[6] Di Rocco C, Battaglia D, Pietrini D, Piastra M, Massimi L. Hemimegalencephaly: clinical implications and surgical treatment. Childs Nerv Syst 2006;22:852–66.
[7] King M, Stephenson JBP, Ziervogel M, Doyle D, Galbraith S. Hemimegalencephaly – a case for hemispherectomy? Neuropediatrics 1985;16:46–55.
[8] Di Rocco C, Iannelli A, Marchese E, Vigevano F, Rossi GF. Surgical treatment of epileptogenic hemimegalencephaly. Minerva Pediatr 1994;46:231–7.
[9] Woo CLF, Chuang SH, Becker LE, Jay V, Otsubo H, Rutka JT, et al. Radiologic–pathologic correlation in focal cortical dysplasia and hemimegalencephaly in 18 children. Pediatr Neurol 2001;25:295–303.
[10] Guerra MP, Cavalleri F, Migone N, Lugli L, Delalande O, Cavazzuti GB, et al. Intractable epilepsy in hemimegalencephaly and tuberous sclerosis complex. J Child Neurol 2007;22:80–4.
[11] Robain O, Chiron C, Dulac O. Electron microscopic and Golgi study in a case of hemimegalencephaly. Acta Neuropathol 1989;77:664–6.
[12] Prayson RA, Bingaman W, Frater JL, Wyllie E. Histopathologic findings in 37 cases of functional hemispherectomy. Ann Diagn Pathol 1999;3:205–12.
[13] Salamon N, Andres M, Chute DJ, Nguyen ST, Chang JW, Huynh MN, et al. Contralateral hemimicrencephaly and clinical-pathological correlations in children with hemimegalencephaly. Brain 2006;129:352–65.
[14] Tinkle BT, Schorry EK, Franz DN, Crone KR, Saal HM. Epidemiology of hemimegalencephaly: a case series and review. Am J Med Genet 2005;139A:204–11.
[15] Sasaki M, Hashimoto T, Shimada M, Iinuma K, Fushiki S, Takano T, et al. Nation-wide survey on hemimegalencephaly in Japan. No To Hattatsu 2000;32:255–60 (in Japanese).
[16] Sasaki M, Hashimoto T, Furushima W, Okada M, Kinoshita S, Fujikawa Y, et al. Clinical aspects of hemimegalencephaly by means of a nationwide survey. J Child Neurol 2005;20:337–441.
[17] Cook SW, Nguyen ST, Hu B, Yudovin S, Shields WD, Vinters HV, et al. Cerebral hemispherectomy in pediatric patients with epilepsy: comparison of three techniques by pathological substrate in 115 patients. J Neurosurg 2004;100:125–41 (Pediatrics 2).
[18] Villemure JG, Mascott CR. Peri-insular hemispherotomy: surgical principles and anatomy. Neurosurgery 1995;37:975–81.
[19] Delalande O, Bulteau C, Dellatollas G, Fohlen M, Jalin C, Buret V, et al. Vertical parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a population of 83 children. Neurosurgery 2007;60(ONS Suppl.):ons19–=0?>ons32.
[20] Döring S, Cross H, Boyd S, Harkness W, Neville B. The significance of bilateral EEG abnormalities before and after hemispherectomy in children with unilateral major hemisphere lesions. Epilepsy Res 1999;34:65–73.
[21] Limbrick Jr DD, Narayan P, Powers AK, Ojemann JG, Park TS, Bertrand M, et al. Hemispherotomy: efficacy and analysis of seizure recurrence. J Neurosurg Pediatr 2009;4:323–32.
[22] Smith SJM, Andermann F, Villemure JG, Rasmussen TB, Quesney LF. Functional hemispherectomy: EEG findings, spiking from isolated brain postoperatively, and prediction of outcome. Neurology 1991;41:1790–4.
[23] Carreño M, Wyllie E, Bingaman W, Kotagal P, Comair Y, Ruggieri P. Seizure outcome after functional hemispherectomy for malformations of cortical development. Neurology 2001;57:331–3.
[24] Cats EA, Kho KH, van Nieuwenhuizen O, van Veelen CWM, Gosselaar PH, van Rijen PC. Seizure freedom after functional hemispherectomy and a possible role for the insular cortex: the Dutch experience. J Neurosurg 2007;107:275–80 (4 Suppl. Pediatrics).
[25] Kwan A, Ng WH, Otsubo H, Ochi A, Snead III OC, Tamber MS, et al. Hemispherectomy for the control of intractable epilepsy in childhood: comparison of 2 surgical techniques in a single institution. Neurosurgery 2010;67 [ons429–ons36].
[26] Boshuisen K, van Schooneveld MMJ, Leijten FSS, de Kort GAP, van Rijen PC, Gosselaar PH, et al. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. Neurology 2010;75:1623–30.
[27] Hallbook T, Ruggieri P, Adina C, Lachhwani DK, Gupta A, Kotagal P, et al. Contralateral MRI abnormalities in candidates for hemispherectomy for refractory epilepsy. Epilepsia 2010;51:556–63.
[28] Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62:1712–21.
[29] Chiron C, Raynaud C, Jambaqué I, Dulac O, Zilbovicius M, Syrota A. A serial study of regional cerebral blood flow before and after hemispherectomy in a child. Epilepsy Res 1991;8:232–40.
[30] Soufflet C, Bulteau C, Delalande O, Pinton F, Jalin C, Plouin P, et al. The nonmalformed hemisphere is secondarily impaired in young children with hemimegalencephaly: a pre- and postsurgery study with SPECT and EEG. Epilepsia 2004;45:1375–82.
[31] Curtiss S, de Bode S, Mathern GW. Spoken language outcomes after hemispherectomy: factoring in etiology. Brain Lang 2001;79:379–96.
[32] Rintahaka PJ, Chugani HT, Messa C, Phelps ME. Hemimegalencephaly: evaluation with positron emission tomography. Pediatr Neurol 1993;9:21–8.
[33] Battaglia D, Di Rocco C, Iuvone L, Acquafondata C, Iannelli A, Lettori D, et al. Neuro-cognitive development and epilepsy outcome in children with surgically treated hemimegalencephaly. Neuropediatrics 1999;30:307–13.
[34] Pulsifer MB, Brandt J, Salorio CF, Vining EPG, Carson BS, Freeman JM. The cognitive outcome of hemispherectomy in 71 children. Epilepsia 2004;45:243–54.
[35] de Bode S, Firestine A, Mathern GW, Dobkin B. Residual motor control and cortical representations of function following hemispherectomy: effects of etiology. J Child Neurol 2005;20:64–75.

CASE REPORT

Neurol Med Chir (Tokyo) 53, 47～52, 2013

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.

Received August 10, 2011; Accepted November 28, 2011

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

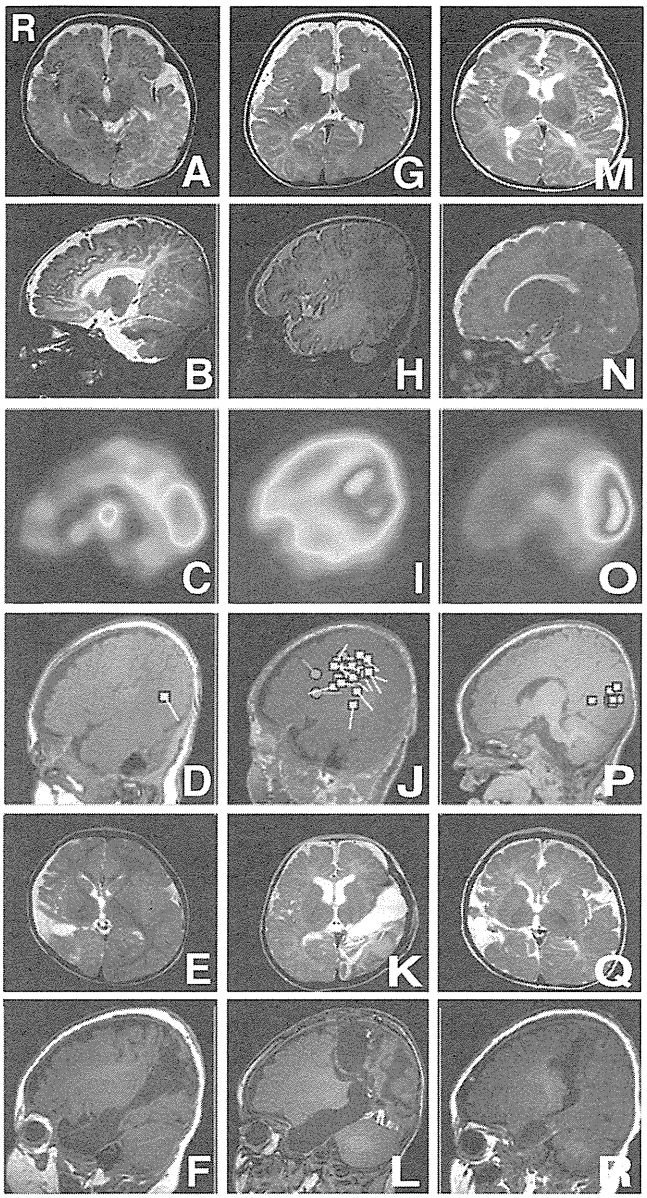

Fig. 1 Neuroimages of Case 1 (A–F), Case 2 (G–L), and Case 3 (M–R). A, B, G, H, M, N: Magnetic resonance (MR) images demonstrating temporoparietooccipital cortical dysplasias. C, I, O: Ictal single photon emission computed tomography scans. D, J, P: Magnetoencephalography with superimposition onto sagittal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

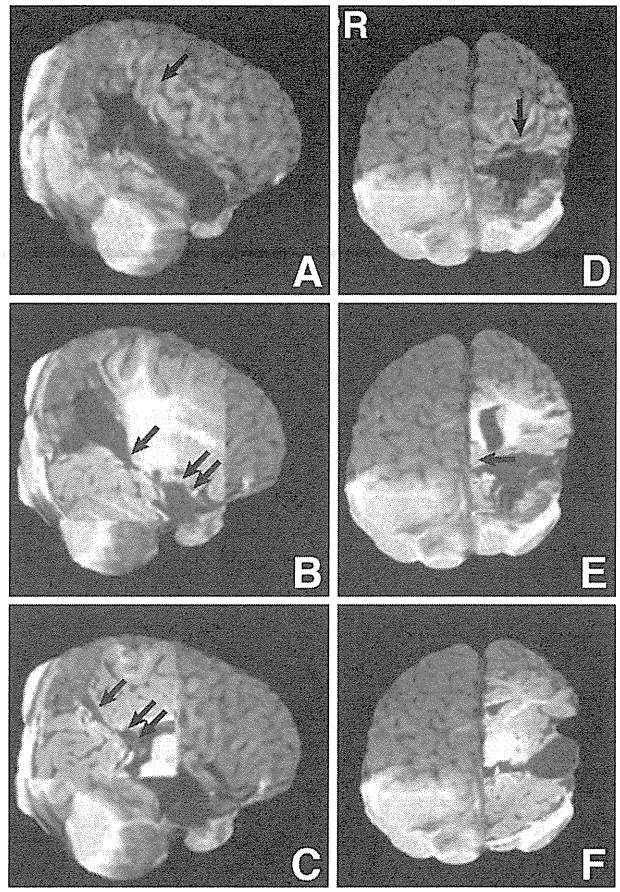

Fig. 2 Postoperative three-dimensional surface rendering magnetic resonance images in Case 1. A–C: Lateral view; D–F: axial view; B, C, E, F: cut-out images of the brain (right upper quadrant). A: Surface rendering image showing the periinsular window. The temporal pole, the temporal opercular cortex, 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.

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 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.

Acknowledgments

This work was supported by a Key Science and Technology Program of Shaanxi Province, China (Grant No. 2009K18-02). We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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.

References

1) Bingaman WE: Surgery for focal cortical dysplasia. *Neurology* 62(6 Suppl 3): S30-34, 2004
2) Bjornaes H, Stabell KE, Heminghyt E, Roste GK, Bakke SJ: Resective surgery for intractable focal epilepsy in patients with low IQ: predictors for seizure control and outcome with respect to seizures and neuropsychological and psychosocial functioning. *Epilepsia* 45: 131-139, 2004
3) D'Agostino MD, Bastos A, Piras C, Bernasconi A, Grisar T, Tsur VG, Snipes J, Juhasz C, Chugani H, Guerrini R, Cross H, Andermann E, Dubeau F, Montes J, Olivier A, Andermann F: Posterior quadrantic dysplasia or hemihemimegalencephaly: a characteristic brain malformation. *Neurology* 62: 2214-2220, 2004
4) Daniel RT, Meagher-Villemure K, Farmer JP, Andermann F, Villemure JG: Posterior quadrantic epilepsy surgery: technical variants, surgical anatomy, and case series. *Epilepsia* 48: 1429-1437, 2007
5) Daniel RT, Meagher-Villemure K, Roulet E, Villemure JG: Surgical treatment of temporoparietooccipital cortical dysplasia in infants: report of two cases. *Epilepsia* 45: 872-876, 2004
6) Diaz RJ, Sherman EM, Hader WJ: Surgical treatment of intractable epilepsy associated with focal cortical dysplasia. *Neurosurg Focus* 25(3): E6, 2008
7) Duchowny M, Jayakar P, Resnick T, Harvey AS, Alvarez L, Dean P, Gilman J, Yaylali I, Morrison G, Prats A, Altman N, Birchansky S, Bruce J: Epilepsy surgery in the first three years of life. *Epilepsia* 39: 737-743, 1998
8) Fauser S, Bast T, Altenmuller DM, Schulte-Monting J, Strobl K, Steinhoff BJ, Zentner J, Schulze-Bonhage A: Factors influencing surgical outcome in patients with focal cortical dysplasia. *J Neurol Neurosurg Psychiatry* 79: 103-105, 2008
9) Fish DR, Smith SJ, Quesney LF, Andermann F, Rasmussen T: Surgical treatment of children with medically intractable frontal or temporal lobe epilepsy: Results and highlights of 40 years' experience. *Epilepsia* 34: 244-247, 1993
10) Freitag H, Tuxhorn I: Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. *Epilepsia* 46: 561-567, 2005
11) Holthausen H, Teixeira VA, Tuxhorn I: Epilepsy surgery in children and adolescents with focal cortical dysplasia, in Tuxhorn I, Holthausen H, Boenigk H (*eds*): *Paediatric Epilepsy Syndromes and Their Surgical Treatment*. London, John Libbey, 1997, pp 199-215
12) Leiphart JW, Peacock WJ, Mathern GW: Lobar and multilobar resections for medically intractable pediatric epilepsy. *Pediatr Neurosurg* 34: 311-318, 2001
13) Lortie A, Plouin P, Chiron C, Delalande O, Dulac O: Characteristics of epilepsy in focal cortical dysplasia in infancy. *Epilepsy Res* 51: 133-145, 2002
14) Mathern GW, Giza CC, Yudovin S, Vinters HV, Peacock WJ, Shewmon DA, Shields WD: Postoperative seizure control and antiepileptic drug use in pediatric epilepsy surgery patients: The UCLA experience, 1986-1997. *Epilepsia* 40: 1740-1749, 1999
15) Mohamed AR, Freeman JL, Maixner W, Bailey CA, Wrennall JA, Harvey AS: Temporoparietooccipital disconnection in children with intractable epilepsy. *J Neurosurg Pediatr* 7: 660-670, 2011
16) Novegno F, Massimi L, Chieffo D, Battaglia D, Frassanito P, Bianco LF, Tartaglione T, Tamburrini G, Di Rocco C, Guzzetta F: Epilepsy surgery of posterior quadrant dysplasia in the first year of life: experience of a single centre with long term follow-up. *Seizure* 20: 27-33, 2011
17) Olavarria G, Petronio JA: Epilepsy surgery in infancy. *Pediatr Neurosurg* 39: 44-49, 2003
18) Palmini A, Gambardella A, Andermann F, Dubeau F, da Costa JC, Olivier A, Tampieri D, Robitaille Y, Paqlioli E, Paqlioli Neto E: Operative strategies for patients with cortical dysplastic lesions and intractable epilepsy. *Epilepsia* 35 Suppl 6: S57-S71, 1994
19) Wyllie E: Surgery for catastrophic localization-related epilepsy in infants. *Epilepsia* 37 Suppl 1: S22-S25, 1996
20) Wyllie E, Comair YG, Kotagal P, Raja S, Ruggieri P: Epilepsy surgery in infants. *Epilepsia* 37: 625-637, 1996

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

ELSEVIER

Brain & Development 35 (2013) 786–792

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Clinical analysis of catastrophic epilepsy in infancy and early childhood: Results of the Far-East Asia Catastrophic Epilepsy (FACE) study group ☆

Hirokazu Oguni [a,*], Taisuke Otsuki [b], Katsuhiro Kobayashi [c], Yushi Inoue [d], Eiji Watanabe [e], Kenji Sugai [f], Akio Takahashi [b], Shinichi Hirose [g], Shigeki Kameyama [h], Hitoshi Yamamoto [i], Shinichiro Hamano [j], Koichi Baba [k], Hiroshi Baba [l], Seung-Chyul Hong [m], Heung-Dong Kim [n], Hoon-Chul Kang [n], Guoming Luan [o], Tai-Tong Wong [p]

[a] *Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan*
[b] *Department of Neurosurgery, National Center Hospital of Neurology and Psychiatry, Kodaira, Japan*
[c] *Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Okayama, Japan*
[d] *National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan*
[e] *Department of Neurosurgery, Jichi Medical University, Tochigi, Japan*
[f] *Department of Pediatric Neurology, National Center Hospital of Neurology and Psychiatry, Kodaira, Japan*
[g] *Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan*
[h] *Department of Functional Neurosurgery, Epilepsy Center, Nishi-Niigata Chuo National Hospital, Niigata, Japan*
[i] *Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki, Japan*
[j] *Department of Neurology, Saitama Children's Medical Center, Japan*
[k] *Department of Neurosurgery, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan*
[l] *Department of Neurosurgery, National Nagasaki Medical Center, Nagasaki, Japan*
[m] *Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea*
[n] *Department of Pediatrics, Pediatric Epilepsy Clinics, Severance Children's Hospital, Epilepsy Research Center, Yonsei University College of Medicine, Seoul, Republic of Korea*
[o] *Department of Neurosurgery, Sanbo Brain Institute, Beijing, China*
[p] *Department of Neurosurgery, Taipei Veterans General Hospital and School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*

Received 8 November 2012; received in revised form 7 February 2013; accepted 12 February 2013

Abstract

Purpose: We studied children younger than 6 years old who developed catastrophic epilepsy and were registered in the FACE study group to clarify their clinical characteristics and prevalence of seizure as well as epilepsy types. Subjects: Subjects were prospectively recruited from children with epilepsy who satisfied the following criteria and underwent intensive examination between 2009 and 2012 in 14 collaborative centers: (1) younger than 6 years old and (2) more than 10 seizures/month refractory to all available medical treatments including ACTH therapy, leading to significant psychosocial morbidity. Methods: We analyzed epilepsy onset age, predominant seizure type, etiology, neuropsychological findings, and syndromic classification according to

☆ Part of this work has been presented at the International Symposium on Surgery for Catastrophic Epilepsy in Infants (ISCE), the Fourteenth Annual Meeting of ISS, Tokyo, February 18–19, 2012.

* Corresponding author. Address: Department of Pediatrics, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162, Japan. Tel.: +81 3 3353 8111; fax: +81 3 5269 7338.
E-mail address: hoguni@ped.twmu.ac.jp (H. Oguni).

http://dx.doi.org/10.1016/j.braindev.2013.02.004

the pre-determined registration format. Results: A total of 314 children were enrolled in this study. Epilepsy onset age in 239 cases (80%) was younger than 12 months. The most frequent seizure type was epileptic spasms (ES), followed by generalized tonic seizures (GTS), which accounted for 42% and 20%, respectively. West syndrome (WS) was the most frequent epileptic syndrome and accounted for 37%, followed by unclassified epilepsy at 21%, neocortical epilepsy at 19%, Lennox–Gastaut syndrome at 12%, Dravet syndrome at 4%, Rasmussen syndrome at 2%, and others. The two most frequent causes of epilepsy were cortical dysplasia and chromosomal anomalies, as shown in 16% and 6%, respectively. However, the etiology of nearly one half of all patients remained unknown. Psychomotor development was already worse than a moderate degree in 62% of subjects at the first examination. Conclusion: The highest proportion of catastrophic epilepsy was WS and its related syndromes featuring ES and GTS, followed by neocortical epilepsy, whose psychomotor development was significantly retarded at examinations.

Keywords: Catastrophic epilepsy; Young children; West syndrome; Etiology; Epilepsy surgery; Classification

1. Introduction

The term "catastrophic childhood epilepsy" was first introduced by North American pioneers who began performing epilepsy surgery on children whose seizures begin early in life and were so frequent and intense that their psychomotor development and daily life were significantly impaired [1–4]. Because of the impact that catastrophic seizure disorders have on a child's life and the lack of effective antiepileptic drugs, new therapies are especially needed for this group of patients [5]. However, the earlier that epilepsy develops, the more severe and malignant the nature of that epilepsy, the etiology of which is serious and diverse from neurometabolic disorders such as mitochondrial encephalopathy to acquired structural brain abnormalities such perinatal hypoxic–ischemic encephalopathy [6–8]. Therefore, it is true that the outcome of catastrophic epilepsy largely depends on the etiology of patients rather than the treatment strategy. However, it is still also true that the control of epileptic seizures or epileptic encephalopathy may contribute to better developmental outcomes irrespective of the etiology. Although the most recent ILAE proposal has not recommended using the term "catastrophic" because it sounds hopeless for families, we have tried new treatment strategies to release these groups of patients from catastrophes [9]. However, no systematic survey has been globally undertaken so far on the epidemiology and treatment prognoses of these patients. Since patients with catastrophic epilepsy are relatively rare and are referred to specialized pediatric epilepsy centers, an international multicenter study among these major pediatric epilepsy centers is needed. Therefore, we conducted a multi-institutional study including 14 collaborative Asian centers to reveal the clinical characteristics of this patient group.

2. Subjects

Subjects were children with highly refractory epilepsy who satisfied the following criteria and underwent an extensive examination at one of the 14 collaborative hospitals or institutions participating in the Far-East Asia Catastrophic Epilepsy (FACE) study group.

(1) Age younger than 6 years old at the first seizure, (2) more than 10 seizures/month refractory to more than two antiepileptic drugs and ACTH therapy, resulting in the stagnation/deterioration of psychomotor development, (3) extensive examinations including ictal and interictal EEG, brain MRI, brain SPECT/PET, developmental assessments, and cytogenetic studies if required during admission, and (4) patients with nonepileptic conditions, atypical forms of benign epilepsy, and severe non-cerebral physical co-morbidities were excluded. Patients were prospectively collected during the registration period between 2009 and 2012, according to the predetermined registration format (Table 1S).

3. Methods

All data including brain MRI, EEG, seizure, and epileptic syndrome classifications, as well as psychomotor development at the time of investigation, were evaluated in each hospital according to the registration format and were used for this analysis. We analyzed ages at the onset of epilepsy, etiology, main seizure type classification based on the 1981 International Classification of Epileptic Seizures [10], and syndrome classifications based on the 1989 International Classification of Epilepsy [11] and Epileptic syndromes and psychomotor development at the time of first examination. Seizure type classification was made either based on the ictal video-EEG examinations or clinical grounds if it was difficult to apply because of infrequent seizures.

Psychomotor development was assessed according to the Tsumori/Inage, Enjoji, and Vineland and KIDS test for those in other countries. All results were categorized to normal ($\geqslant 80$), borderline to mild delay (<80, $\geqslant 70$), moderate delay (<60, $\geqslant 50$), severe delay (<49, $\geqslant 35$), most severe delay (<34, $\geqslant 20$), and extremely severe disabling (<20) according to the developmental quotient. Tanaka-Binet Japan-made IQ tests were applied for Japanese patients who were able to respond to this test.

The proposed protocol was approved by the Ethics Review Board of each hospital participating in the

FACE study group prior to the start of the study. Written informed consent was obtained from the participants in each hospital or institution before the registration.

4. Results

A total of 314 children (boys: 185, girls: 129) who fulfilled the criteria were enrolled in this study. The onset age of epilepsy was between 0 and 6 months in 185 patients or 58.9%, between 7 and 12 months old in 60 patients or 19.1%, and older than 12 months in the remaining 69 patients or 22.0%. Thus, in a total of 245 cases or 78% of all patients, epilepsy developed at or younger than 12 months old (Fig. 1).

4.1. Etiology

The etiology of epilepsy was estimated from past histories, and brain MRI, CT, and cytogenetic findings. It consisted of cortical dysplasia, which accounted for 16%, hypoxic–ischemic encephalopathy of a largely perinatal origin (the period from 28th week of gestation through the 7th day after birth) for 11%, tuberous sclerosis for 7%, other cytogenetic abnormalities for 5%, central nervous system infection for 5%, vascular lesions for 4%, and others (Table 1). Thus, 28.5% of all patients had prenatal origins, and another 29% had postnatal origins. However, the etiology was still unknown in the remaining 42% of patients.

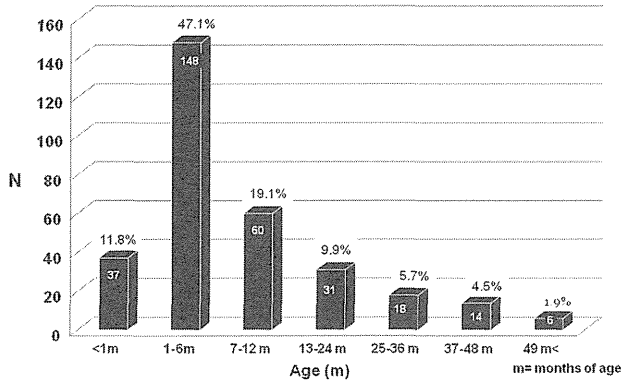

Fig. 1. Age at the onset of epilepsy ($n = 314$). Age at the onset of epilepsy in 185 patients or 58.9% was between 0 and 6 months old, and that in 60 patients or 19.1% was between 7 and 12 months old. Thus, in a total of 245 cases or 78% of all patients, epilepsy developed at or younger than 12 months.

Table 1
Etiology ($n = 314$).

	N	%
Cortical dysplasia	49	16
Hypoxic encephalopathy	33	11
Tuberous sclerosis	23	7
Genetic/chromosomal abnormalities	17	5
Infection	14	5
Vascular lesions	13	4
Tumors	3	1
Head trauma	3	1
Hemimegalencephaly	2	0.5
Other miscellaneous	23	7
Unknown	132	42
Not described	2	0.5
Total	314	100

4.2. Seizure type classification

A total of 73% of all patients had generalized seizures and the remaining 22% had focal seizures. The most frequent seizure type was epileptic spasms (ES), which comprised 37%, followed by generalized tonic seizures (GTS) in 20%, and partial complex motor seizures in 15%. Thus, ES and GTS were the main seizure types in at least 57% of all patients (Fig. 2).

4.3. Epileptic syndrome classification

At the time of investigation, the most frequent epileptic syndrome was West syndrome, which accounted for 36%, followed by unclassified epilepsy at 21%, neocortical epilepsy at 19%, Lennox–Gastaut syndrome (LGS) at 11%, Dravet syndrome at 4%, Rasmussen syndrome at 2%, and Ohtahara syndrome (OS), myoclonic-astatic epilepsy (Doose syndrome), and Sturge–Weber syndrome at 1% each (Fig. 3). Patients with neocortical epilepsy, unclassified epilepsy, and LGS included a total of 36 cases (11%) with a history of WS. Thus, a total of 47% of patients were classified into West syndrome and its related syndromes.

The unclassified epilepsy group ($n = 66$) formed the second largest group, accounting for 21% of all patients. Forty-four of these cases (67%) developed their first seizure at the age of 12 months or younger. Eight cases had a history of WS. The most disabling seizure type was GTS in 25 cases, followed by ES and head nodding attacks in 7, complex motor seizures in 6, and partial simple in 5. Interictal EEG showed generalized or multifocal epileptic abnormalities in 49 cases. Thus, more than half of the patients with unclassified epilepsy were categorized into some form of diffuse epileptic encephalopathy featuring ES or GTS and generalized or multifocal epileptic EEG abnormalities unclassifiable for either WS or LGS.

The third largest group was neocortical epilepsy ($n = 60$), accounting for 19% of all patients. Seventy-three percent of these cases developed their first seizure at an age of less than 12 months. Focal and generalized seizures accounted for 63% and 37%, respectively. The most disabling seizure types consisted of partial complex motor seizures in 31 cases, followed by hypomotor seizures in 6, and partial simple motor seizures in one. The etiology of epilepsy comprised focal cortical dysplasia, which accounted for 13%, generalized cortical dysplasia for 5%, hypoxic–ischemic encephalopathy for