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Resective Pediatric Epilepsy Surgery in Lennox-Gastaut Syndrome

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Resective Pediatric Epilepsy Surgery in Lennox-Gastaut Syndrome

WHAT'S KNOWN ON THIS SUBJECT: Epilepsy surgery can be performed successfully for selected patients who have suffered LGS with generalized EEG abnormalities.

WHAT THIS STUDY ADDS: In addition, resective epilepsy surgery could be considered for children with LGS despite absence of MRI lesions and the surgical treatment improved in cognitive and developmental aspects as well as seizure outcomes.

abstract

OBJECTIVE: The objective of this study was to evaluate the role of resective pediatric epilepsy surgery for Lennox-Gastaut syndrome (LGS).

METHODS: We analyzed clinical data of 27 children and adolescents who had LGS and underwent resective epilepsy surgery despite abundant (>30% of preoperative interictal and/or ictal epileptiform discharges) generalized or generalized contralateral maximal and multiregional electroencephalogram abnormalities.

RESULTS: On high-resolution MRI, cerebral lesions were noted in 23 (85.2%) patients but not in 4 (14.8%) patients. The age of patients at the time of surgery was between 1.7 and 17.3 years (mean: 7.8 years). Surgeries were lobar or multilobar resection in 21 (77.8%) patients and hemispherotomy in 6 (22.2%). At a mean of 33.1 months' postoperative follow-up, 16 (59.3%) patients had no seizures and 4 (14.8%) had infrequent seizures. Of 4 patients without brain abnormalities found on MRI, 2 patients became seizure-free after resective surgery was performed on the basis of electrophysiologic studies and concordant results in other multimodal neuroimages. Malformation of cortical development was the most common pathology and was seen in 20 (74.1%) patients, but 2 (7.4% patients) did not show any abnormal pathology. Sixteen (72.7%) patients, including 14 who had no seizures and 2 who had infrequent seizures after surgery, showed an increase in developmental quotient. No clinical profile was significantly associated with postoperative seizure-free rate.

CONCLUSIONS: Resective epilepsy surgery should be considered for children with LGS, despite abundant generalized and multiregional electroencephalogram abnormalities. *Pediatrics* 2010;125:e58–e66

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KEY WORDS

Lennox-Gastaut syndrome, epilepsy surgery

ABBREVIATIONS

LGS—Lennox-Gastaut syndrome
EEG—electroencephalogram
PET—positron emission tomography
FDG—F18-labeled fluorodeoxyglucose
SPECT—single photon emission computed tomography
MRS—magnetic resonance spectroscopy
DTI-FT—diffusion tensor imaging-fiber tractography
NAA—*N*-acetyl aspartate
Cr—creatine plus phosphocreatine
Cho—choline-containing compounds
SSFA—spindle-shaped fast activities
PLPS—persistent localized polymorphic slowings
FSSA—focal subclinical seizure activities
LPFA—localized paroxysmal fast activities
BIRD—brief ictal rhythmic discharges
MCD—malformation of cortical development
DQ—developmental quotient

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Lennox-Gastaut syndrome (LGS) is 1 of the most intractable catastrophic epilepsies in children, characterized by multiple types of generalized seizures, interictal bilaterally synchronous slow spike waves and paroxysmal fast activity in the electroencephalogram (EEG), and progressive cognitive impairment.[1,2] Most patients with LGS have bilateral diffuse encephalopathy, but focal lesions that cause secondary generalized epileptic encephalopathy can be identified by other EEG findings, MRI, and functional neuroimaging studies. Of course, we might expect that successful resective epilepsy surgery provides better outcomes both in seizure reduction and in developmental progress in these patients. Recently, Cleveland's group reported successful outcomes of resective epilepsy surgery for children with brain MRI lesions, despite abundant generalized and multiregional EEG abnormalities.[3,4] Here, we analyzed clinical data of patients who had LGS and underwent resective pediatric epilepsy surgery despite abundant generalized and multiregional EEG abnormalities and expanded our experience to include cryptogenic LGS without brain MRI abnormalities.

METHODS

Of 235 pediatric epilepsy surgeries at Severance Children's Hospital during 2001–2007, we identified 27 patients who had LGS and underwent resective pediatric epilepsy surgery, despite abundant generalized and multiregional EEG abnormalities. LGS is defined by clinical triads of (1) multiple generalized seizure types, including tonic, atonic, myoclonic seizures, atypical absences, and spasms; (2) generalized slow spike-and-wave and/or generalized paroxysmal fast activities in EEG findings; and (3) progressive mental deficiency. The criterion for the percentage of interictal/ictal generalized or generalized contralateral maximum or interictal multiregional epileptiform discharges was >30% referenced to a previous report by Wyllie et al.[3] Patients who showed ictal contralateral epileptiform discharges were rejected for epilepsy surgery. All patients had frequent daily disabling seizures, 1 to 120 per day (mean ± SD: 17.3 ± 26.5), that were not adequately controlled by ≥3 drugs (median: 3.9) for >1 year. Previously, a ketogenic diet was attempted with 7 patients but failed. Two patients had an active vagus nerve stimulator device (Cyberonics, Houston, TX).

Presurgical evaluation was conducted with long-term video/EEG monitoring (Grass-Telefactor system [Telefactor Corp, Conshohoken, PA]), MRI with epilepsy protocol, positron emission tomography (PET) with F18-labeled fluorodeoxyglucose (FDG), interictal/ictal single photon emission computed tomography (SPECT) after intravenous injection of 99mTc-ethylcysteinated diamer, magnetic resonance spectroscopy (MRS), diffusion tensor imaging and fiber tractography (DTI-FT), and detailed clinical history and neurologic examination. Our MRI with epilepsy protocol included the following sequences: sagittal T1-weighted images, axial and coronal T2-weighted images and fluid-attenuated inversion recovery, and coronal volumetric 3-dimensional Fourier-acquired steady state with thin (1.6- to 2.0-mm) thickness. Single-volume 1H spectra were obtained from a 1.5 × 1.5 × 1.5-cm voxel within focal suspected lesions and from the contralateral remote cortex as a control, and the ratios of the main visible metabolites, *N*-acetyl aspartate (NAA), creatine plus phosphocreatine (Cr), and choline-containing compounds (Cho) were measured. DTI was also performed by using a single-shot spin echo-echo planar imaging, with navigator echo phase correction and sensitivity encoding factor 2.

Intracranial recording by grids and strips was done for 21 patients with planning for single or multilobar resection to determine the margin of resection and to localize the eloquent area. For 4 patients without brain MRI abnormalities, phase II study proceeded after confirmation that ictal semiology was concordant to lateralized patterns of video/EEG monitoring and functional neuroimaging studies. Histopathologic examinations followed the classification of Palmini et al.[5]

Seizure outcome was assessed by Engel's classification[6] at the time of last visit during the minimum of 12 months (mean: 33.1 months) of follow-up. Comprehensive evaluation of preoperative and postoperative cognitive function and development were performed by (1) the neuropsychological developmental scale assessments by a psychologist and (2) global developmental assessment by caregivers. Both preoperative and postoperative developmental scale assessment data were available for 22 children with Bayley Scales of Infant Development, Korean-Wechsler Preschool and Primary Scales of Intelligence, Korean-Wechsler Intelligence Scale for Children, and Korean-Wechsler Adults Intelligence Scale. Postoperative developmental assessments were repeated every 6 to 12 months during follow-up, and the last follow-up data were used for comparison with the patients' preoperative status. Finally, we analyzed the relationship between postoperative seizure outcomes and preoperative clinical data, including age at seizure onset or surgery, duration of epilepsy before surgery, seizure type, type of MRI lesion, and type of surgery.

SPSS 13.0 for Windows (SPSS, Inc, Chicago, IL) was used for statistical regression analysis and multivariate data analysis, and 2-tailed χ^2 testing and Student's *t* test were used to evaluate significant differences of depen-

dent, categorical, and continuous variables. $P < .05$ was regarded as statistically significant.

RESULTS

Patient Profiles

The ages of 27 patients (16 boys, 11 girls) at surgery ranged from 1.7 to 17.3 years (mean ± SD: 7.8 ± 3.7 years). The duration between seizure onset and surgery of epilepsy ranged from 1.4 to 11.8 years (mean ± SD: 5.9 ± 3.9 years). The duration of follow-up after surgery was between 12.0 and 51.6 months (mean ± SD: 33.1 ± 20.3 months; Table 1). Patients showed numerous seizure types, and the main and concomitant seizure types are summarized in Table 1. Eight (29.6%) patients had seizure onset by infantile spasms.

TABLE 1 Demographic Profiles

Parameter	Value
Gender, male:female, *n* (%)	16 (59.3):11 (40.7)
Age at seizure onset, *n* (%), y	
<1	13 (48.1)
1–5	11 (40.7)
≥5	3 (11.1)
Mean ± SD	2.0 ± 2.8
Range	0.3–12.0
Age at surgery, *n* (%), y	
<5	8 (29.6)
5–10	12 (44.4)
≥10	7 (25.9)
Mean ± SD	7.8 ± 3.7
Range	1.7–17.3
Mean duration of seizure onset to the surgery, y	
Mean ± SD	5.9 ± 3.9
Range	1.4–11.8
Mean follow-up duration after surgery, mo	
Mean ± SD	33.1 ± 20.3
Range	12.0–51.6
Seizure types, *n* (%)	
Main seizure types	
Atonic seizures	11 (40.7)
Convulsive (GT/GC/GTC) seizures	10 (37.0)
Myoclonic seizures	5 (18.5)
Atonic and myoclonic seizures	1 (3.7)
Concomitant seizure types	
Spasms	3 (11.1)
Partial seizures	3 (11.1)
Absence seizures	2 (7.4)

GT indicates generalized tonic; GC; generalized clonic; GTC; generalized tonic clonic.

Presurgical Evaluation

Of the 27 patients, 23 (85.2%) had focal or unilateral lesions on MRIs. Focal cortical dysplasia was the most common finding and was observed in 18 (66.7%) patients. Four patients had extensive encephalomalacia, and 1 had unilateral cerebral infarction. Even after using detailed application of high-resolution MRI techniques, 4 (14.8%) patients were determined to be nonlesional (Table 2).

Long-term video/EEG monitoring showed abundant generalized and multiregional epileptiform discharges and characteristic focal or unilateral interictal EEG findings, especially around MRI lesions, which suggested focal epileptogenic zones (Table 3). Of these, the rate of concordance with focal epileptogenic zones defined by the final surgical resection areas and surgical outcomes was the highest, 100% (8 of 8), in spindle-shaped fast activities (SSFA), persistent localized polymorphic slowings (PLPS) were found in 96.0% (24 of 25), focal subclinical seizure activities (FSSA) were found in 87.5% (7 of 8), localized paroxysmal fast activities (LPFA) were found in 83.3% (10 of 12), focal/multifocal spikes or sharp waves were found in 74.1% (20 of 27), and brief ictal rhythmic discharges (BIRD) were found in 66.7% (2 of 3). Particularly, in the brains of the 4 patients without brain MRI lesions, PLPS, LPFA, and SSFA were observed in 4, 3, and 3 patients, respectively, and concordant to focal epileptogenic zones in 4, 2, and 3 patients, respectively.

All patients underwent FDG-PET scans. Of 23 patients with brain MRI abnormalities, focal hypometabolism was concordant with the focal epileptogenic zones in 18 patients. Of 4 patients without brain MRI abnormalities, focal hypometabolism was concordant to epileptogenic zones in 3 patients. Ictal SPECT could be obtained for 11 patients and was concordant in 8 patients, including 1 patient without brain MRI abnormalities, and nonfocal in 3 patients. By typical reduction in NAA/Cho or NAA/Cr in the region of focal cortical dysplasia, MRS could confirm focal cortical dysplasia in 3 patients with brain MRI abnormalities, but the ratio of NAA/Cho or NAA/Cr were not lateralized in 4 patients, including 2 patients without abnormalities found on brain MRI. DTI-FT revealed abnormal tract formation around focal brain MRI lesions in 7 (50.0%) of 14 patients (Table 4).

Epilepsy Surgery and Outcomes

Ten (37.0%) patients underwent multilobar resection. Eleven (40.7%) patients underwent single lobar resection: frontal in 10 patients and temporal in 1 patient. Functional hemispherotomies were performed in 6 (22.2%) patients.

Of 27 patients, Engel's class I outcomes (no seizures) were achieved in 16 (59.3%) patients and class II outcomes (infrequent seizures) were achieved in 4 (14.8%) patients. Eight (29.6%) patients who had no seizures could discontinue anticonvulsant medications. An additional 2 (7.4%) patients had class III (worthwhile improvement), and 5 (18.5%) patients had class IV (no significant reduction in seizure frequency). According to types of surgery, 83.3% who underwent hemispherotomy, 60.0% who underwent multilobar resection, and 45.5% who underwent single lobe resection obtained Engel's class I outcomes (Fig 1).

In 4 patients with normal brain MRI findings, 2 patients who underwent frontal resection achieved Engel's class I outcomes. The other 2 patients

TABLE 2 Neuroradiologic, Pathologic, and Surgical Characteristics and Seizure Outcomes

Patient	Brain MRI Findings	Pathology	Etiology	Timing of Lesion	Age at Epilepsy Onset, y/mo	Age at Surgery, y/mo	Surgery	Outcome: Engel's class
1	CD	CD	MCD	Congenital	0/3	5/0	Lt TO	I
2	CD	CD	MCD	Congenital	0/3	2/0	Lt T	I
3	CD	CD	MCD	Congenital	3/0	13/1	Lt FT	I
4	CD	CD	MCD	Congenital	0/3	8/5	Lt TO	I
5	CD	CD	MCD	Congenital	0/10	9/0	Rt H	I
6	CD	CD	MCD	Congenital	2/1	6/4	Lt F	II
7	CD	CD	MCD	Congenital	1/5	7/4	Rt FT	IV
8	CD	CD	MCD	Congenital	2/8	7/7	Lt F	IV
9	CD	CD	MCD	Congenital	0/3	9/7	Lt F	IV
10	CD	Microdysgenesis	MCD	Congenital	12/0	17/4	Rt F	I
11	CD	Microdysgenesis	MCD	Congenital	2/6	5/0	Lt H	I
12	CD	Microdysgenesis	MCD	Congenital	7/2	13/4	Rt TO	I
13	CD	Microdysgenesis	MCD	Congenital	1/5	4/3	Lt FT	I
14	CD	Microdysgenesis	MCD	Congenital	0/3	1/11	Lt F	I
15	CD	Microdysgenesis	MCD	Congenital	0/6	8/11	Lt H	I
16	CD	Microdysgenesis	MCD	Congenital	0/10	11/10	Lt FT	II
17	CD	Microdysgenesis	MCD	Congenital	2/0	13/10	Rt F	III
18	CD	Microdysgenesis	MCD	Congenital	0/5	2/0	Rt FT	III
19	Encephalomalacia	Gliosis	Encephalitis	10 mo	0/10	10/0	Lt H	I
20	Encephalomalacia	Gliosis + HS	Sepsis	4 mo	0/7	4/11	Lt TO	I
21	Encephalomalacia	Gliosis	Encephalitis	8 y	8/0	12/11	Lt FT	II
22	Encephalomalacia	—	Sepsis	3 d	1/11	9/2	Lt H	II
23	Infarction	Microdysgenesis	MCD	Congenital	1/0	3/0	Lt H	I
24	Nonlesional	Microdysgenesis	MCD	Congenital	1/8	3/6	Rt F	IV
25	Nonlesional	Gliosis	Encephalitis	3 mo	0/4	9/10	Rt F	IV
26	Nonlesional	Nonspecific	Cryptogenic	—	1/0	7/5	Lt F	I
27	Nonlesional	Nonspecific	Cryptogenic	—	0/4	4/11	Lt F	I

CD indicates cortical dysplasia; HS, hippocampal sclerosis; Lt, left; Rt, right; F, frontal; T, temporal; O, occipital; H, hemispherotomy.

TABLE 3 Focal EEG Findings

EEG Findings	*n* (%)	Concordant, *n* (%)[a]
Focal/multifocal spikes or sharp waves	27 (100.0)	20 (74.1)
PLPS	25 (92.6)	24 (96.0)
LPFA	12 (44.4)	10 (83.3)
SSFA	8 (29.6)	8 (100.0)
FSSA	8 (29.6)	7 (87.5)
BIRD	3 (11.1)	2 (66.7)

[a] Defined by the final surgical resection areas and surgical outcomes.

in whom frontal resection was performed did not have any reduction of seizure frequency. In patients without MRI findings, primary epileptogenic cortex was localized by electrophysiologic findings and multimodal neuroimagings. In these patients, long-term video/EEG monitoring showed localized excitable and/or dysfunctional EEG findings, such as PLPS, LPFA, SSFA, and FSSA. In 2 patients who showed excellent postoperative results, these data were concomitantly supported by other preoperative diagnostic modalities, such as FDG-PET (2 patients), interictal SPECT (1 patient), or DTI-FT (1 patient); however, 1 of 2 patients with poor surgical outcome had concordant but somewhat diffuse hypometabolic area in FDG-PET and disconcordant findings in DTI-FT, and the other patient also had discordant findings in FDG-PET. The detailed preoperative diagnostic data are summarized in Table 5. In addition, 2 representative patients with and without MRI abnormalities, respectively, are presented in Figs 2 and 3.

TABLE 4 Additional Neuroimaging Findings

Neuroimaging Technique	*n*	Concordant, *n* (%)	Discordant, *n* (%)	Nonfocal, *n* (%)
PET	27	21 (77.8)	3 (12.5)	3 (12.5)
SPECT				
Interictal	23	15 (65.2)	1 (4.3)	7 (30.4)
Ictal	11	8 (72.7)	0 (0.0)	3 (27.3)
1H-Spectroscopy	7	3 (42.9)	0 (0.0)	4 (57.1)
DTI-FT	14	7 (50.0)	1 (7.1)	6 (42.9)

Malformations of cortical development (MCDs) were the most common pathologic findings in 20 (74.1%) patients and included microdysgenesis in 11 (40.7%) patients and focal cortical dysplasia in 9 (33.3%) patients. Nonspecific gliosis was found in 3 (11.1%) patients, and gliosis plus hippocampal sclerosis was found in 1 (3.7%) patient. It is intriguing that 2 (7.4%) patients had no specific pathologic findings, although both patients achieved Engel's class I outcomes after surgery. Brain specimen was not obtained for 1 patient, who underwent

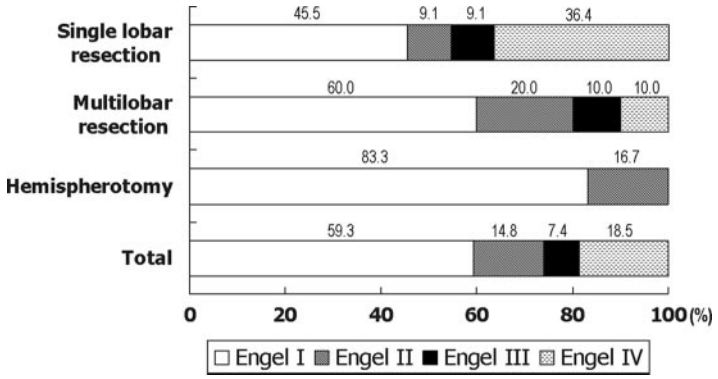

FIGURE 1
Postoperative seizure outcomes based on Engel's classification according to surgery types.

hemispherotomy (Table 2). Concerning the time of the acquisition of the brain lesions, 74.1% (20 of 27) of patients had MCDs, which would construe as being congenital, whereas the extensive encephalomalacia seen in 14.8% (4 of 27) was acquired in the neonatal period or infancy (aged 3 days to 1 year). Only 1 patient acquired extensive encephalomalacia in childhood (at 8 years). We could not estimate the time of the initial evolution in 2 children who had nonlesional MRI findings and no pathologic lesions (Table 2).

Routine scalp EEG was serially followed up by at least ≥1 episode at ~3 to 6 months after resective surgery in 27 patients. Naturally, the EEG findings were well correlated to the outcomes of seizure frequency. Of 20 patients who had Engel's class I or II, most of the 18 patients showed improvement in background activity and 5 patients obtained normalization of them. Although favorable seizure outcomes of 20 patients were achieved, generalized epileptiform discharges with LPFA remained in 3 patients, and localized epileptiform discharges lasted in an additional 2 patients (SSFA in 1 patient and BIRD in 1 patient).

Of 22 patients for whom developmental scale assessments by a psychologist could be followed up, 16 (72.7%), including 14 who had Engel's class I outcome and 2 patients with Engel's class II outcomes, showed increases in developmental quotient (DQ). Six of them showed a significant increase—>15 points—in DQ after surgery. As per our expectations, seizure outcome was well correlated to improvement of DQ (Table 6). All 20 patients with favorable outcomes and another patient with Engel's class III outcome (21 [77.8%] of 27) had improved scores in global developmental assessments performed by parents or caregivers. Unfortunately, caregivers of 2 (7.4%) of 27 patients, 1 classified as Engel's class III and another as Engel's class IV, reported that their global development was deteriorated after surgery.

Of presurgical data, including age at seizure onset, duration of epilepsy before surgery, seizure type, type of MRI lesion, and type of surgery, we could not find any significant data associated with seizure outcomes after resective surgery. In terms of complications of resective epilepsy surgery, expected hemianopia occurred in 1 (3.7%) patient after occipital resection and accepted hemiplegia was observed in 2 (7.4%) patients after hemispherotomy. There were 3 (11.1%) patients in whom minor infarction occurred around the motor cortex and showed weakness of contralateral upper extremity, but fortunately all recovered within 6 months. As minor events, 5 (18.5%) patients had hematomas as a result of postoperative hemorrhage, and they were spontaneously absorbed without reoperation. No mortality was reported in our surgical patients.

DISCUSSION

We described here that resective pediatric epilepsy surgery for LGS with abundant generalized and multiregional EEG abnormalities may be successful for selected patients with or even without focal brain MRI lesions. After early reports of successful surgery for selected children with infantile spasms and hypsarrythmia by several groups,[7–9] the Cleveland group recently reported excellent outcomes of resective epilepsy surgery in children and adolescents with a congenital or early-acquired brain lesion and generalized EEG abnormalities.[3,4] They identified 10 children with exclusively

TABLE 5 Presurgical Evaluation and Surgical Outcomes of the 4 Patients Without Brain MRI Abnormalities

Patient	PET	SPECT Interictal/Ictal	DTI-FT	Focal EEG Findings				Surgery	Engel's Class
				PLPS	LPFA	SSFA	FSSA		
24	Conc but diffuse (Rt FC)	Discor (both F)/—	Discor (both F)	Conc	Discor (both F)	Conc	Conc	Rt F	IV
25	Discor (Rt PQ)	Conc/Conc	—	Conc	—	—	—	Rt F	IV
26	Conc	Conc/—	Conc	Conc	Conc	Conc	—	Lt F	I
27	Conc	—/—	—	Conc	Conc	Conc	—	Lt F	I

Conc indicates concordant; Discor, discordant; Rt, right; Lt, left; F, frontal; FC, frontocentral; PQ, posterior quadrant.

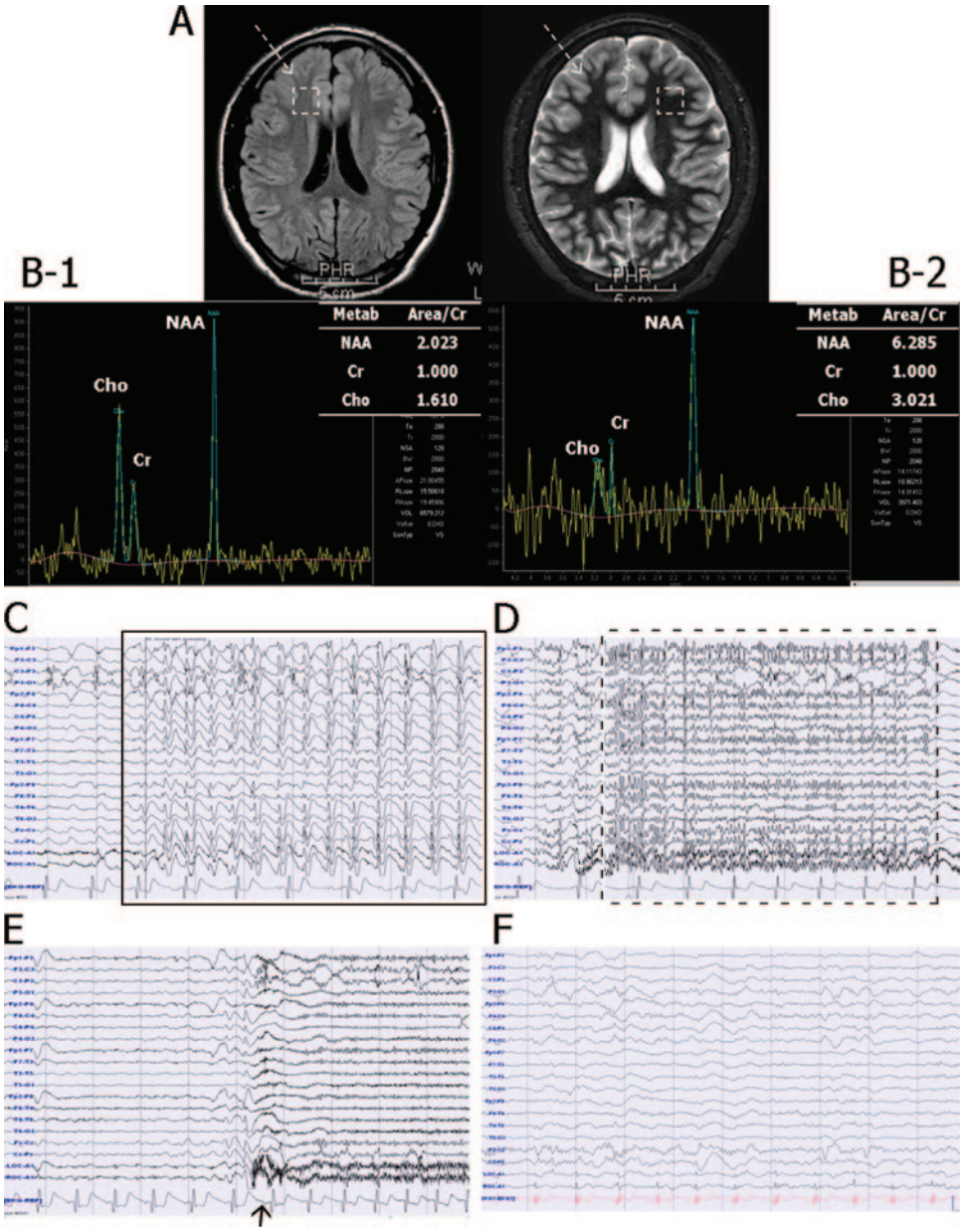

FIGURE 2

A 16-year-old boy with moderate mental impairment (IQ of 45) had refractory epilepsy since 12 years of age. Seizures presented as generalized tonic seizures of both arms for 10 to 15 seconds, 5 to 6 times per day. All available antiepileptic medications could not suppress his seizures. He underwent a right frontal lobectomy at 17 years of age and has been free of seizures for 2.5 years without medication. A, Axial T1- and T2-weighted MRI shows a blurring of the gray-white matter interface on the right frontal area (arrows). FDG-PET also showed focal hypometabolism on the right frontal lobe (data not shown). B1 and B2, 1H spectroscopy could confirm focal cortical dysplasia by typical reduction of ratio of NAA to Cr from a voxel within the right frontal lobe (B1, box on right frontal area) compared with that from the contralateral remote cortex as a control (B2, box on left frontal area). C and D, Baseline interictal awake EEG shows contralateral localized epileptiform discharges and exclusively generalized epileptiform discharges, such as generalized slow spike and waves (solid line) and generalized paroxysmal fast activities (dotted line). During the interictal burst, there was no change in his behavior. E, Ictal EEG shows generalized slow waves followed by low-voltage fast activities (arrow) during generalized tonic seizure. F, EEG 15 months after surgery showing nearly normalized background activities and no epileptiform discharge. Referencing longitudinal montage (Fp1-F3, F3-C3, C3-P3, P3-O1/Fp2-F4, F4-C4, C4-P4, P4-O2/Fp1-T1, T1-T3, T3-T5, T5-O1/Fp2-T2, T2-T4, T4-T6, T6-O2/Fz-Cz, Cz-Pz/EMG1, EMG2, EKG) for all EEG features.

generalized or multiregional interictal and ictal EEG abnormalities, and all patients achieved Engel's class I or II outcomes.[4] In another series, they reported that of 50 patients in whom 30% to 100% of preoperative epileptiform discharges were generalized or contralateral to the side of surgery, 88% had no seizures or had marked improvement.[3] We focused on patients with LGS because it is the representative intractable catastrophic epilepsy

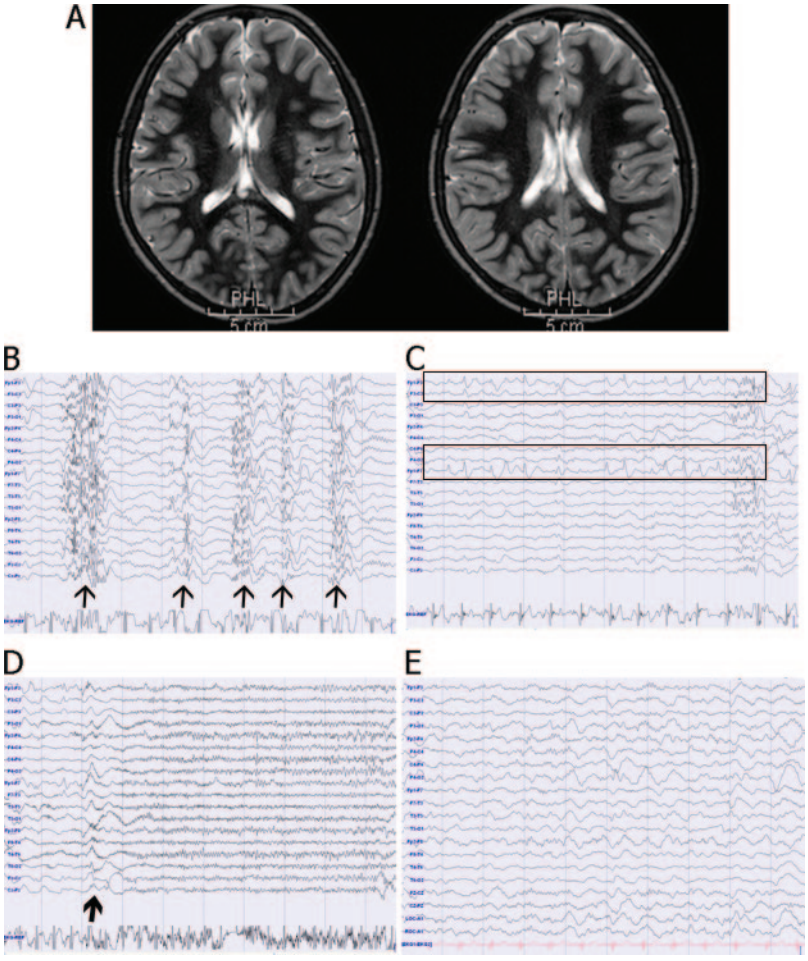

FIGURE 3

A 9-year-old boy with severe developmental delay correlated with cognition of approximately a 2-year-old and intractable epilepsy since 18 months of age. Seizures were presented as abrupt head drop without injury 20 to 30 times per day. His seizure frequency did not decrease despite all possible antiepileptic medications and corpus callosotomy. He underwent a left frontal lobectomy at 9 years of age and has been seizure-free for 3 years while only taking valproate. A, Axial T2-weighted MRI shows no abnormal lesions. FDG-PET had a focal hypometabolism on the left frontal lobe (data not shown). B and C, Baseline interictal awake EEG shows exclusively generalized paroxysmal fast activities (arrows) and persistent localized slow spike and waves and LPFA (solid line) on the left frontal area. D, Ictal EEG shows generalized slow waves (thick arrow) during clinical seizure with sudden head drop. E, EEG after left frontal lobectomy shows no focal or generalized epileptiform discharges. Referencing longitudinal montage (Fp1-F3, F3-C3, C3-P3, P3-O1/Fp2-F4, F4-C4, C4-P4, P4-O2/Fp1-T1, T1-T3, T3-T5, T5-O1/Fp2-T2, T2-T4, T4-T6, T6-O2/Fz-Cz, Cz-Pz/EMG1, EMG2, EKG) for all EEG features.

TABLE 6 Comparison of DQ Scores According to Surgical Outcome Between Before and After Surgery

Engel's Classification	Mean DQ		*P*
	Before Surgery	After Surgery	
I ($n = 14$)	42.71	51.93	.0002
II ($n = 3$)	41.67	49.67	NS
III ($n = 2$)	37.00	46.50	NS
IV ($n = 3$)	32.67	32.67	NS
Total ($n = 22$)	40.70	48.50	.0010

NS indicates no significance.

in older children and is characterized by secondary generalized epileptic encephalopathy. By referencing the criteria of a previous report,[3] we also identified 27 patients who had LGS and in whom >30% of preoperative epileptiform discharges were generalized and/or generalized contralateral maximum or multiregional epileptiform discharges. In our surgical series, however, patients who showed ictal contralateral discharges were rejected for epilepsy surgery. Among 27 patients, 74% had no or infrequent seizures after surgery and showed a similarity to previous experiences. In the Cleveland group's surgical series, all patients had epileptogenic focal lesions on brain MRI, predominantly MCDs.[3]

Here, we expanded our observations to include 4 patients without brain MRI abnormalities. Successful seizure freedom in patients without findings on MRI was 50.0% (2 of 4), which was comparable to the postsurgical seizure freedom of 60.8% (14 of 23) in patients with findings on MRI. In patients without findings on MRI, localization was based primarily on long-term video/EEG findings, but in 2 patients who showed excellent postoperative results, these data were concomitantly supported by other preoperative neuroimages, such as FDG-PET, SPECT, or DTI-FT. In the 2 patients who did not achieve a favorable outcome, concordance with other presurgical evaluations was not consistent. It is a noticeable phenomenon that consistently concordant multimodal neuroimages helped to establish correct decisions in patients without MRI abnormalities.[10]

We also demonstrated by preoperative and postoperative developmental scale assessments that 72.7% of the patients who had no or infrequent seizures after surgery showed a significant increase in DQ. Infants or younger children with catastrophic-onset epilepsy may undergo widespread developmental damage, and early successful surgical therapy in these patients may prevent irreversible deterioration in cognitive function and global development.[7,11,12] Here, we could also confirm that surgical intervention for older children and adolescents with LGS that caused epileptic encephalopathy also provided a valuable opportunity to prevent irreversible deterioration of cognitive function.[13,14]

Cleveland's group suggested that the most outstanding age-related variable was not the age at presurgical evaluation and surgery but the age at event of the brain lesions.[3] Mechanisms are unknown, but the generalized and contralateral epileptiform discharges can be made by potentially secondary epileptogenesis[15] resulting from an interaction between the early lesion and the developing brain. In our study, direct comparison of outcome according to the age at acquisition of the symptomatic lesions was unattainable, and we plan to follow up on this variable in the future.

It is known that many forms of focal electrographic abnormalities could be instigated from primary and secondary epileptogenic regions.[16,17] These localized EEG findings include PLPS, SSFA, LPFA, FSSA, and BIRD, and their significances are varied among previous reports, especially when regarding secondary generalized epileptic encephalopathies, where most epileptiform discharges are generalized.[8,18] Patients who had Engel's class I or II outcomes had marked reduction or disappearance of characteristic focal EEG findings and interictal generalized EEG abnormalities. These focal EEG findings were very useful in screening underlying pathology.

Focal hypometabolism of PET, perfusion pattern of ictal/interictal SPECT, MRS, and DTI-FT findings were highly concordant to focal brain MRI lesions and could support ictal semiology and lateralized patterns of video/EEG monitoring to determine the area for intracortical recording. Lee et al[19] reported that DTI-FT has a high potential to localize the subtle cortical dysplasia; however, functional neuroimagings and DTI-FT did not yield additional significant information in our patients with brain MRI lesions. Conversely, for the patient without lesions detected by brain MRI, PET and ictal/interictal SPECT were important diagnostic modalities to proceed to phase II study.

MCDs are the main cause of intractable childhood epilepsy, and common findings include focal cortical dysplasia, periventricular heterotopia, band heterotopia, polymicrogyria, and microdysgenesis.[17,20,21] Clinical features of patients with MCDs have frequently been associated with early seizure onset and poor seizure outcome by medication.[22,23] In our study, MCDs were also the most common finding in patients with brain MRI lesions. Even in 2 patients without brain MRI abnormalities, postoperative pathologic findings demonstrated microdysgenesis in 1 patient and gliosis in 1 patient. Two other patients who did not have brain MRI lesions and achieved Engel's class I outcomes after surgery had no specific pathologic findings according to the classification of Palmini et al.[5] From our observation, pathologic examination of epileptogenic cortex sometimes has limitations to elicit the discrete underlying cortical hyperexcitability. Mild cortical dysplasia was defined as ectopically placed neurons in or adjacent to the first cortical layer or microscopic neuronal heterotopia outside the layer,[5] but the criteria for diagnosing MCDs is still controversial, and its revision is still required.

A toddler's brain may manifest with generalized epileptiform discharges in response to focal brain lesions, whereas an infant's brain presents with infantile spasms and hypsarrythmia in response to similar lesions.[4] Mechanisms that are responsible for the generalized EEG abnormalities in children with congenital or early-acquired brain lesion remains to be discovered. There have been several hypotheses, including maladaptive neural plasticity, abnormal network synchronization, and circuit alterations by kindling.[24,25]

CONCLUSIONS

Our data demonstrated that epilepsy surgery for selected patients with LGS can be successful despite generalized EEG abnormalities and absence of MRI lesions. In addition to the seizure outcome, the surgical treatment rendered improvement in cognitive and developmental aspects; however, additional long-term follow-up is necessary to validate the cognitive and developmental benefits after resective epilepsy surgery in LGS.

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