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Cognitive and epilepsy outcomes after epilepsy surgery caused by focal cortical dysplasia in children: early intervention maybe better

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Abstract
Background Focal cortical dysplasia (FCD) is a specific malformation of cortical development harboring intrinsic epileptogenicity, and most of the patients develop drug-resistant epilepsy in early childhood. The detrimental effects of early and frequent seizures on cognitive function in children are significant clinical issues. In this study, we evaluate the effects of early surgical intervention of FCD on epilepsy outcome and cognitive development.
Methods From 2006 to 2013, 30 children younger than 18 years old underwent resective surgery for FCDs at Taipei Veterans General Hospital. The mean age at surgery was 10.0 years (range 1.7 to 17.6 years). There were 21 boys and 9 girls. In this retrospective clinical study, seizure outcome, cognitive function, and quality of life were evaluated. To evaluate the effects to outcomes on early interventions, the patients were categorized into four groups according to age of seizure onset, duration of seizure before surgery, and severity of cognitive deficits.
Results Eleven of 22 (50 %) patients demonstrated developmental delay preoperatively. The Engel seizure outcome achievements were class I in 21 (70 %), class II in 2 (7 %), class III in 6 (20 %), and class IV in 1 (3 %) patients. The locations of FCDs resected were in the frontal lobe in 18 cases, temporal lobe in 7, parietal lobe in 2, and in bilobes including frontoparietal lobe in 2 and parieto-occipital lobes in 1. Eight cases that had FCDs involved in the rolandic cortex presented hemiparesis before surgical resection. Motor function in four of them improved after operation. The histopathological types of FCDs were type Ia in 1, type Ib in 7, type IIa in 7, type IIb in 12, and type III in 3 patients. FCDs were completely resected in 20 patients. Eighteen (90 %) of them were seizure free ($p<0.001$) with three patients that received more than one surgery to accomplish complete resection. The patients who

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had early seizure onset, no significant cognitive function deficit, and early surgical intervention with complete resection in less than 2 years of seizure duration showed best outcomes on seizure control, cognitive function, and quality of life.
Conclusion Delay in cognitive development and poor quality of life is common in children treated for FCDs. Early surgical intervention and complete resection of the lesion help for a better seizure control, cognitive function development, and quality of life. FCDs involved eloquent cortex may not prohibit complete resection for better outcomes.

Keywords Cognitive function · Childhood epilepsy · Epilepsy surgery outcome · Focal cortical dysplasia · Quality of life

Introduction

Focal cortical dysplasia (FCD) is a spectrum of structurally and functionally abnormal cortical dysplastic lesions capable of intrinsic epileptogenesis. Successful resection and subsequent characterization of FCD were first described by Taylor et al. in 1971 from pathological specimens of lobectomy obtained in ten epileptic patients [1]. The classification of FCD did not reach consensus until the task force of the International League Against Epilepsy (ILAE) Diagnostic Methods Commission proposed a unified one in 2011 [2].

Currently, little is known about the pathophysiological basis of the epileptiform activity, but the influence of the neuronal population and perilesional changes in the neurochemical profile are considered to be major epileptogenic mechanisms [3].

FCD is recognized by its histological attributes, which include blurring of the gray-white matter junction, cortical dyslamination, and/or the presence of abnormal balloon cells in the cortical and subcortical regions. In most patients with epilepsy, the disease became refractory to medical therapy [4, 5]. Therefore, surgical intervention is usually indicated, but some previous studies have documented unsatisfactory epilepsy surgery outcomes in this group of patients [6–10]. Due to the enormous progression in neuroimaging and multimodality emerging techniques, the FCD becomes more visible to delineate in preoperative study, and therefore surgery is once again increasing in recent decade [11–14].

The detrimental effect of frequent early seizures on the cognitive potential of children and the concept of neuronal plasticity are significant clinical issues too [15–21]. The aims of the present study were to investigate the cognitive function, epilepsy outcome, and quality of life of epilepsy surgery for FCD in children and to determine predictive factors influencing cognitive development. In particular, evidence for postoperative catch-up of development and better quality of life would provide a good rationale for earlier timing of surgical intervention.

Material and methods

From 2006 to 2013, 30 children (<18 years old) underwent resective epilepsy surgery with histopathologically confirmed diagnosis of FCD at the Taipei Veterans General Hospital. Two cases of hemimegalencephaly and two cases with tuberous sclerosis complex were excluded. There were 9 female and 21 male patients whose mean age at first resective surgery was 9.95 years (range, 1.7 to 17.6), age at seizure onset ranged from 1 month to 9 years (mean, 3.2 years), and mean duration of epilepsy before first resective surgery was 6.7 years (range, 0.1 to 17.2). The mean duration of their follow-up was 21.5 months (range, 4 to 97).

Presurgical evaluation included continuous scalp video-EEG monitoring, high-resolution magnetic resonance imaging (MRI), and functional imaging modalities including (SPECT/PET and functional MRI) magnetoencephalography (MEG) and neuropsychological assessment. The children in this study had at least one follow-up at 4 to 12 months after surgery, including neurological examination, EEG, MRI, and neuropsychological assessment.

The parameters for the early MRI differed from those of the more recent examinations, with better imaging details on the more recent sequences. The available results of PET were fused with 3D and 2D MRI of the brain. Following implantation of subdural electrodes, patients underwent computerized tomography scanning, and the results of which were superimposed on MRI to assess electrode location. Patients then underwent extraoperative seizure monitoring and functional mapping performed using the implanted depth and subdural electrode for 5 to 7 days. All patients' preoperative data were discussed in a multidisciplinary epilepsy surgery conference.

For patients with involvement of the rolandic area, we performed preoperative functional MRI for evaluation of the motor unit reorganization and discussion of the risk of postoperative deterioration. Intraoperative neurophysiological monitoring (motor evoked potential and somatosensory evoked potential) was used to confirm whether resection over the rolandic cortex was acceptable or not.

Seizure outcome, neuropsychological assessment, adaptability, and quality of life

The outcomes of seizures and neurological function were obtained from patients' charts and telephone interviews. We

categorized seizure outcomes using Engel's four-category classification consisting of class I, free of disabling seizures; class II, rare disabling seizures; class III, worthwhile improvement; and class IV, no worthwhile improvement [22].

Cognitive development was assessed preoperatively and postoperatively by a developmental neuropsychologist. We used the Wechsler intelligence test for children who were older than 3.5 years and the Bayley Scales of Infant and Toddler Development—Third Edition for those younger than 3.5 years old or with limited language expression. Twenty-four (80 %) patients received at least one time of developmental quotient/intelligence quotient (DQ/IQ) evaluation. DQ (100×cognitive developmental age/chronological age) was obtained from seven patients. One of them was older than 10 years old but with limited or no speech and only followed simple commands. Five of them were younger than 3.5 year old. Two of them scored within the normal range, and the other three were developmentally delayed (DQ ranged from 10 to 56).

Two sets of questionnaire, Adaptive Behavior Assessment System (ABAS-II) and Child Health Questionnaire (CHQ-PF50), were also included to measure daily life adaptability and the quality of life after epilepsy surgery in these FCD patients.

According to the cognitive development of patients, onset age, and duration of seizure, we categorized the FCD patients into four groups consisting of group 1, seizure onset before age of six and seizure duration less than 2 years; group 2, seizure onset after age of six regardless of seizure duration; group 3, seizure onset before age of six and seizure duration longer than 2 years with mild deficits in cognitive function (IQ or DQ >40); and group 4, seizure onset before age of six and seizure duration longer than 2 years with severe impairment in cognitive function (IQ or DQ <40).

Statistical analysis

Fisher's exact test and chi-squared test were conducted to compare the favorable (Engel class I/II) and the poor (Engel class III/IV) outcome with the following: (1) seizure characteristics including patient age at the time of seizure onset and duration of seizures, (2) presence of FCD on MR or PET images, (3) location of resection (temporal lobe, extratemporal lobe, and multiple lobes), (4) cases with intracranial video-EEG or not, and (5) histological feature (FCD type and balloon cells).

Data of cognitive ability and developmental status were analyzed by using variance to compare preoperative and postoperative scores. Linear regression analyses were performed to determine predictors of preoperative and changes in postoperative cognitive function. Data were analyzed with SPSS 20.0.

Results

Surgical procedures

Twenty-six patients underwent lesionectomy guided by neuroimaging navigation, ECoG, and intraoperative neurophysiologic monitoring if it involved the rolandic area. The other four patients underwent evaluation with intracranial monitoring prior to resection due to "invisible" lesion from MRI (all frontal lobe epilepsy with PET-documented hypometabolism). We used a combination of grids, strips, and depth electrodes for an intracranial study.

Seizure outcome

Twenty-one (70 %) patients achieved Engel class I, two (7 %) Engel class II, six (20 %) Engel class III, and one (3 %) Engel class IV. For 20 patients who were followed up for more than 1 year after the last epilepsy surgery, 12 (60 %) patients were Engel class I, 1 (5 %) was Engel class II, 6 (30 %) were Engel class III, and 1 (5 %) was Engel class IV. There were 18 frontal FCD, 7 temporal FCD, 2 parietal FCD, and 3 bilobes FCD (2 frontoparietal and 1 parieto-occipital). Eight cases involved the rolandic area with preoperative hemiparesis, and four cases among them improved of neurological deficits after epilepsy surgery. According to the new ILAE classification of FCD in 2011 [2], the histopathology was type Ia in 1 patient, type Ib in 7, type IIa in 7, type IIb in 12, and type III in 3. Eighteen (90 %) of 20 patients in whom resection of FCD was complete experienced seizure-free outcome ($p<0.001$), and 3 of 18 patients received more than one surgery to accomplish completeness. The seizure-related profile and outcomes of the 30 patients are summarized in Table 1.

Six patients had seizure duration less than 2 years before surgery. All of them are seizure free and four patients discontinued antiepileptic drugs successfully. The pathology was FCD type IIb in four patients and FCD type Ib in two. The outcome of cognitive function and quality of life among them were normal and good.

Eight patients had FCD, and epilepsy involved the rolandic area with contralateral motor weakness before surgery. Preoperative functional MRI was used to evaluate if there was normal functional anatomy despite the presence of the FCD. Intraoperative brain mapping confirmed patterns of corticospinal projections during resective epilepsy surgery. The results were concordant in five cases between functional MRI and intraoperative neuromonitoring. All eight patients achieved complete resection of FCD without moderate or severe deterioration of their motor function due to neuronal reorganization (Table 2).

Five patients (16 %) required repeated operations after the initial surgery failed to control their epilepsy adequately (three patients) or relapse with initial seizure freedom for more than

Table 1 Summary of seizure profiles and seizure-related outcomes of 30 patients

Characteristics	Engel class I/II (%)	Engel class III/IV (%)
Age at seizure onset	11 (79)	3 (21)
<2 years old	12 (75)	4 (25)
≥2 years old		
Duration of seizures	6 (100)	0 (0)
<2 years	17 (71)	7 (29)
≥2 years		
EEG recordings	20 (77)	6 (23)
Intraop ECoG	3 (75)	1 (25)
Intracranial video-EEG		
Presence of balloon cells	10 (83)	2 (17)
Yes	13 (72)	5 (28)
No		
FCD type I	6 (75)	2 (25)
FCD type II	15 (79)	4 (21)
FCD type III	2 (67)	1 (33)
Location of resection	7 (100)	0 (0)
Temporal lobe	14 (70)	6 (30)
Extratemporal lobe	2 (67)	1 (33)
Multilobes lesionectomy		
Complete resection*	19 (95)	1 (5)
Yes	4 (40)	6 (60)
No		

ECoG electrocorticography, *FCD* focal cortical dysplasia

*$p<0.001$(statistically significant)

1 year (two patients). Three of them were finally Engel class I, and the other two improved from Engel class IV to III.

Preoperative cognitive function

For 22 (73 %) patients who received at least one time of DQ/IQ evaluation before resection, there were 11 (50 %) patients below 70. The distribution of patients with preoperative cognitive levels showed 27 % of average intelligence, and there was an obvious shift to the left of the distribution of cognitive function in the studied patients compared to normal distribution (Fig. 1).

Fifteen patients had an average presurgical IQ score of 78.80 (SD=16.82), which was below average. Their performance of the intelligence test including verbal comprehension ($t=-4.02$, $p=0.001$), visual organization ($t=-3.99$, $p=0.001$), working memory ($t=-3.76$, $p=0.002$), processing speed ($t=-7.04$, $p=0.002$), and visual short-term memory test ($t=-8.15$, $p<0.001$) significantly differed from the normative mean. The presurgical average of IQ/DQ of these patients showed slight declination ($M=72.65$, SD=28.90). And, their cognitive performance was significantly correlated with extensiveness of the epileptic activity in the brain region. The patients with extensive brain region of abnormal activity would show significant lower cognitive performance than a focal case ($t=2.98$, $p=0.012$).

Postoperative changes in cognitive development and quality of life

For 14 patients who received both preoperative and postoperative evaluation, only two cases showed mild reduction in post-op 1 year F/U (DQ 40 to 35, IQ 64 to 53) and five cases demonstrated mild to moderate improvement (including two cases that showed initial reduction). Preoperative normal DQ/IQ or profound retard would remain no significant change postoperatively. Five of them received the developmental assessment (Bayley-III) and nine patients received intelligence test. The overall performance of cognitive function was below average (mean=65.91, $t=-3.47$, $p=0.004$). Adaptive function was also constrained due to their physical or

Table 2 Characteristics and clinical findings of the eight patients with FCD and epilepsy-involved rolandic area

Case	Age/sex	Clinical findings	FCD type	CSP in functional MRI	CSP in IONM	Resective location	Post-op motor function	Engel class
1	3/B	Todd's paralysis	IIb	Preserved crossed projection (reorganized posteriorly)	Nil	Motor cortex	Weaker big toe	I
2	13/G	CH	IIb	Bilateral	Failed	Inferior rolandic cortex	Transient weaker paretic hand	II
3	9/B	CH and MR	IIa	Bilateral	Bilateral	Rolandic cortex	Much improved	I
4	4/B	CH and MR	IIb	Ipsilateral	Ipsilateral	Frontoparietal lobes	Improved	I
5	15/G	CH and MR	Ib	Bilateral	Bilateral	Frontal lobe	Premotor syndrome for 2 weeks	I
6	17/B	Clumsy hand and MR	IIb	Preserved crossed projection	Preserved crossed projection	Inferior somatosensory cortex	Improved	I
7	8/B	CH	IIa	Preserved crossed projection	Preserved crossed projection	Cingulate gyrus	Much improved	I
8	4/B	CH and MR	Ia	Equivocal	Preserved crossed projection	Motor cortex	Transient weaker paretic hand	III

B boy, *G* girl, *CH* contralateral hemiparesis, *MR* mental retardation, *CSP* corticospinal projection, *IONM* intraoperative neurophysiological monitoring

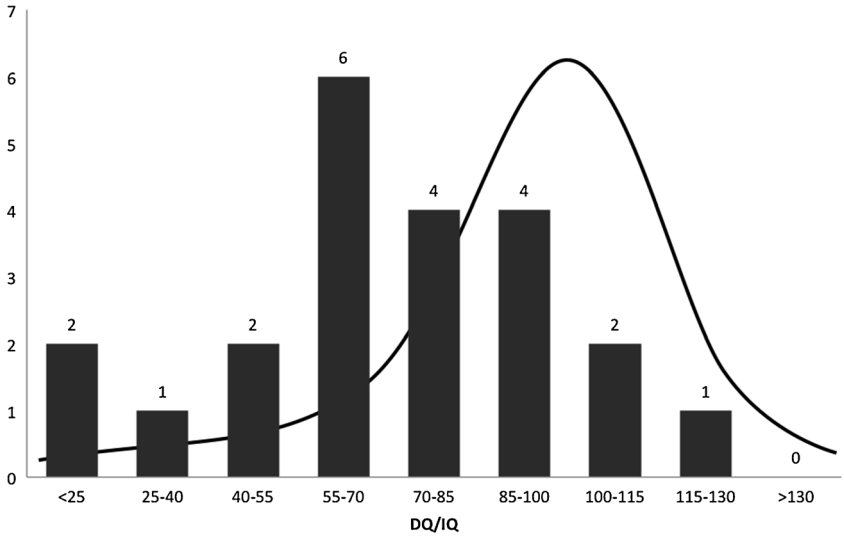

Fig. 1 Preoperative cognitive function compared to normal distribution

cognitive impairment. General adaptive composite score was significantly lower than the average (mean=79.50, t=−2.43, p=0.031). The result of CHQ-PF50 also showed that the quality of life in these families was also in the low average. However, the indexes of physical health summary (mean=39.10, SD=17.85) and psychological health summary (mean=44.84, SD=13.31) were not significantly different from the normal average.

Pearson correlation was adopted to inspect the factors that would affect cognitive outcome, adaptive function, and quality of life, but not a single factor demonstrated significant correlation.

The four groups of FCD patients differed significantly in full-scaled IQ and DQ (Table 3). The first group exhibited the best cognitive outcome. The average IQ of this group stands within average (M=105.00, SD=25.12). The second group scored within normal range but was significantly behind the first group (M=95.67, SD=7.51). Most patients in the third group had mild intellectual disability or scored with the borderline range (M=72.17, SD=16.77). The average cognitive performance of the fourth group was significantly lower than the other three groups (F=19.91, p<0.01). All the patients in the fourth group displayed severe declines across different functional domains, and thus we could only assess their developmental levels through DQ scores (M=19.45, SD=11.72) (Fig. 2).

Parent-reported questionnaires of adaptive function and quality of life suggested that group 1 showed the best outcome as compared to the other three. All the indices of ABAS-II, a questionnaire of adaptive behavior, were above average in group 1. They exhibited various well-adaptive abilities in communication, social skills, and practical skills as typically developing child. The other three groups scored below average in most of the adaptive behavior domains. Group 2 is better than group 3. Most patients in group 4 were still dependent in daily caring and showed least competence in adaptive behavior. This finding was compatible with the results that a positive correlation was found between cognitive performance and adaptive behaviors (r=0.862, p<0.001).

The same trend between the first three groups was observed. However, although patients in group 4 had the most profound cognitive impairment and were largely dependent on caregivers than the other groups, their quality-of-life scores were surprisingly a little higher than group 3. While the severe and frequent seizure attacks were the main concerns of these families before surgery, most patients in group 4 no longer had seizure attack postoperative. Children were easier to take care of and started to learn some basic skills. These improvements in terms of physical and cognitive functioning greatly relieved the burden of caregivers and resulted in better quality of life (Table 3).

Discussion

FCD-related epilepsy is characterized by early onset of age with drug resistance. The developing brain of young children is particularly vulnerable to the epilepsy encephalopathy. Surgical intervention is almost the only chance to cure these patients with freedom of seizure. The functional outcome after surgical resection is one of the most important issues concerned.

In recent years, surgery for FCD was conducted by MRI in the majority of patients with better outcome, esp 3-T MRI with thin-slice no gap protocol. Multimodality approach of MRI, PET, MEG, and fMRI, with or without intracranial EEG, to identify the FCD, epileptogenic region, and eloquent cortex is complementary diagnostic techniques for the best

Table 3 Comparison of cognitive performance, adaptability and quality of life in four groups

	Group 1 Mean (SD)	Group 2 Mean (SD)	Group 3 Mean (SD)	Group 4 Mean (SD)
Cognitive function				
Full scale IQ/DQ[a]	105.50 (25.12)	95.67 (7.51)	72.17 (16.77)	19.45 (11.72)
Adaptive behavior (ABAS-II)				
General adaptive composite[a]	105.50 (20.51)	101.33 (19.55)	67.20 (26.02)	51.50 (14.85)
Conceptual composite[a]	108.50 (16.26)	100.00 (21.07)	66.60 (24.94)	47.00 (4.24)
Communication[b]	12.5 (3.53)	9.67 (4.93)	5.20 (4.15)	1.00 (0.00)
Functional academics[b]	12 (5.65)	9.67 (3.51)	3.80 (4.76)	1.00 (0.00)
Self-direction[b]	13 (4.24)	10.67 (3.79)	3.80 (3.83)	1.50 (0.71)
Social composite[a]	108.50 (16.26)	100.33 (13.58)	71.80 (20.51)	52.00 (4.24)
Leisure[b]	12.00 (5.66)	10.00 (3.00)	4.60 (3.51)	1.50 (0.71)
Social[b]	11.50 (2.12)	10.00 (3.00)	5.20 (3.49)	1.00 (0.00)
Practical composite[a]	102.00 (24.04)	101.00 (20.42)	65.20 (29.69)	50.00 (14.14)
Community use[b]	11.00 (5.66)	10.00 (3.00)	4.20 (5.22)	1.00 (0.00)
Home living[b]	10.00 (4.24)	8.67 (5.86)	3.80 (5.17)	1.00 (0.00)
Health and safety[b]	9.50 (6.36)	12.33 (1.15)	5.20 (4.92)	1.00 (0.00)
Self-care[b]	9.50 (3.54)	9.67 (4.04)	3.80 (4.76)	3.50 (3.54)
Quality of life (CHQ-PF50)				
Physical summary score[c]	49.36 (1.99)	51.17 (4.85)	26.92 (20.32)	35.10 (24.98)
Physical functioning[b]	0.56 (0.00)	0.45 (0.20)	−2.16 (2.76)	−1.82 (3.36)
Role limitation (physical)[b]	0.45 (0.00)	0.16 (0.51)	−3.08 (2.49)	−2.20 (3.74)
General health[b]	−0.67 (1.06)	−0.40 (0.60)	−0.92 (0.46)	−1.51 (1.22)
Bodily pain[b]	0.06 (0.00)	0.39 (0.74)	−0.90 (1.80)	1.03 (0.00)
Psychosocial summary score[c]	61.04 (3.16)	45.71 (2.63)	40.30 (14.68)	36.43 (18.71)
Behavior[b]	0.94 (0.62)	−0.56 (0.28)	−0.66 (0.96)	−1.01 (1.78)
Role limitation (emotion/behavior)[b]	0.49 (0.00)	0.11 (0.33)	−1.93 (1.76)	−2.64 (2.81)
Mental health[b]	1.48 (0.25)	0.45 (0.21)	−0.17 (1.20)	0.02 (0.78)
Self-esteem[b]	0.93 (0.33)	−0.16 (0.14)	−1.58 (1.47)	−1.41 (2.98)
Parent impact (emotion)[b]	0.25 (0.28)	−0.73 (1.03)	−1.12 (2.09)	−1.90 (1.10)
Parent impact (time)[b]	0.79 (0.00)	−1.03 (0.83)	−1.40 (1.73)	−0.85 (1.55)

[a] Mean=100, SD=15, deviation score

[b] Mean=10, SD=3, scale score

[c] Mean=50, SD=10

possible seizure and functional outcome in children [12, 13, 23].

Complete resection of FCD, including surrounding epileptogenic areas, is the most important predictor of seizure outcome [12, 13, 24]. In patients with incomplete excision, seizure recurrence has been related to the extension of dysplastic cortex beyond the visible abnormality [25].

Cognitive impairment in epilepsy patients (esp children) was documented in the early nineteenth century. Cognitive deterioration may take place in a subset of children who have early onset and long duration of epilepsy, and there is a window of vulnerability for irreversible declination [16–21, 26, 27]. Early surgical intervention for epilepsy may have a marked impact on the brain plasticity of children with early-onset and severe epilepsy. Simple partial seizure, even epilepticus partialis, continues, and small gyral lesion would not significantly damage cognitive development but motor function. Children with larger lesions involving one lobe or more were more likely to have preoperative retarded cognition than were those in whom lesions were confined to one or two gyri. This result is in keeping with the results reported by other authors [16, 17].

Shorter duration of seizure before surgery (<2 years) in our series demonstrated excellent result. All six cases were seizure free with normal cognitive function, and four of them discontinued antiepileptic drug. Although all of the six lesions were small in size and confined to single gyrus and the case number was not big enough to achieve statistical significance,

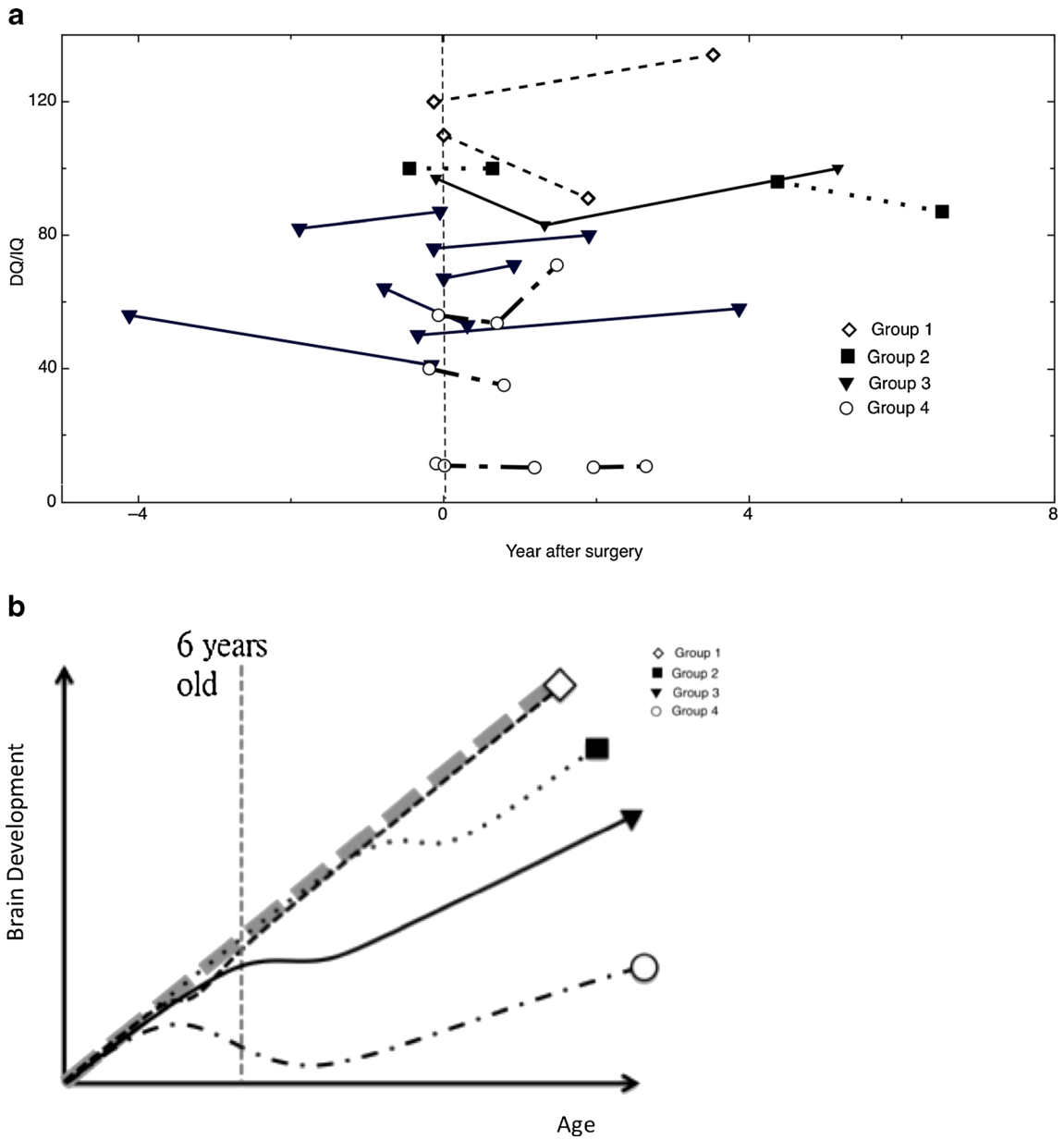

Fig. 2 **a** Change in cognitive performance. **b** Possible cognitive developmental profiles in four groups

it was encouraging for earlier intervention even in normal intelligence patients without risk of deterioration. A shorter duration of epilepsy was the one predictive factor for postoperative long-term gains in cognitive function and brain development [17].

In our study, we divided our patients into four groups according to their age of seizure onset, seizure duration, and preoperative ability. In group 2, patients' IQ scores were within normal range given later onset of seizure. Groups 1, 3, and 4 all included patients with seizure onset earlier than age of six. Patients in group 1 had above average cognitive performance and good quality of life, along with better adaptive functioning to various social settings due to earlier surgical intervention. In contrast, most patients in groups 3 and 4 showed considerable decline in cognitive function and quality of life as consequence of longer seizure duration. Patients in group 3 had relative mild seizure symptom as compared to group 4; nonetheless, as these children suffered from epilepsy for a longer time under the age of 6 years old, their cognitive functioning declined more obviously. As a result, group 3 exhibited relative poorer cognitive outcome and quality of life as compared to groups 1 and 2. Patients in group 4 with the severest type of epilepsy showed the most profound cognitive impairment before surgical intervention. According to our presurgical record, most patients in group 1 who had smaller lesions and more benign epileptic symptoms tended to exhibit fair prognosis even without surgical intervention. However, the significant differences of cognitive abilities between group

1 and groups 3 and 4 still suggest that seizure duration is an important predictive factor of results. At active intervention and at a younger age, the patient became seizure free which not only led to a better outcome (yet, slightly below average) but also gave these children a chance to lead a normal life.

Despite the group categorization, most patients showed some improvements after surgical resection. However, the extent of improvement differed in four groups. Taking collectively the perspectives from neural bases and the stage theory of cognitive development, we attempted to elucidate why the four groups of our patients treated with epilepsy surgery exhibited different cognitive outcomes even when they had become seizure free or not. Although patients in group 1 had early seizure onset (before age of 6 years old), they did not suffer from severe seizure attacks, and the symptoms subsided after surgical intervention in a short period of time (less than 2 years). For these cases, minor cognitive disruption and neural plasticity of the brain led to a better chance for them to catch-up the normal development. Nonetheless, different scenarios were observed in group 3 and group 4. In group 4, seizures attacked frequently, and the effects on development were drastic that impeded the child from acquiring new skills. According to Piaget's developmental theory, the years before age of two is denoted as the "sensorimotor period," in which children construe their knowledge by interaction with the world via sensorimotor activity (e.g., throwing objects or mouthing), which is the basis for development of other more advanced cognitive functions [28]. Due to the age of seizure onset, the abilities of patients in group 4 might somewhat being arrested in the sensorimotor stage. After the surgical intervention, they all showed significant improvements in seizure control. The rate of cognitive development gradually improved as compared to presurgical baselines. However, as the seizures had exerted adverse impacts on the brain development, these children were significantly left behind typically developing children, and the room for improvement is limited. This might explain the observation that patients resumed to learning after seizure freedom but still exhibited a moderate decline in DQ. Patients in group 3 also had an early onset of seizure, but the symptoms and cognitive impairment were not as severe as group 4. Their IQ would increase in most patients after epilepsy surgery. However, patients in group 3 experienced a long period of seizures across toddlerhood into older childhood. Neurocognitive functioning was largely influenced by the abnormal neural activities. Within this group, most patients had mild intellectual disability. Group 2 includes patients with relative late onset of disease (older than 6 years old), which the development of lower-level cognitive processing has completed. Children already possess all basic sensorimotor abilities to interact with the world to develop further cognitive abilities. Despite mild declines in cognitive functioning that sometimes were observed in group 2, their average performance on IQ test was within the normal range. As compared to their strengths in basic cognitive abilities, some higher-order cognitive functions such as reasoning or executive function were more likely to be affected [28–30].

The parents of all five patients received additional surgical resection for the residual FCD after recurrence, or sustained epilepsy expressed tremendous satisfaction about the immediate improvement of their profound developmental delay after staged surgeries although two of them were not seizure free.

PET is more sensitive to MRI in localization of the epileptogenic foci. In our 28 cases with PET study, all of them documented hypometabolic area concordant with histopathologic and epileptogenic lesion (including four extratemporal MRI-negative cases). The hypometabolic area in PET was fused with 3D MRI during surgery, and it was the maximum limitation that we tried not to breakthrough in tailored lesionectomy.

Functional MRI is a noninvasive method for evaluation of neural reorganization preoperatively with resting state connectivity. It can also correlate local functional connectivity by analysis of 26 neighboring voxels to detect intracranial focus of epileptogenicity [31, 32]. It is not uncommon that FCD involves the rolandic area. To remove that part of cortex for better seizure, control is not without the risk of introducing new postoperative deficits [33]. It is frequent that the corticospinal projections of the lesioned hemisphere may have shifted to a new location or the opposite hemisphere since FCD is a congenital disease. Using functional MRI and intraoperative neurophysiological monitoring, the neurological outcome of eloquent area resection is predictable preoperatively, and complete resection of this territory of FCD with improvement of motor function is achievable. We have eight patients of FCD with involvement of the rolandic cortex and presentation of preoperatively contralateral motor weakness (including Todd's paralysis). The seizure outcome was favorable (Engel class I/II) in seven of them due to complete resection of the FCD. Four patients demonstrated either ipsilateral or bilateral corticospinal projections in motor tasks of functional MRI and/or intraoperative brain mapping, and all of them gained improvement of motor function postoperatively with only one patient with transient deterioration (Fig. 3). Four of the eight patients suffered from mild functional deterioration after resection of FCD in motor cortex. Only in one case the deficit was mild and permanent (big toe). Our results of surgery for appropriately selected children with drug-resistance epilepsy due to FCD involving the rolandic cortex were as effective as the previous studies, and the patients would have the chance to gain improvement in both motor and cognitive function [33–35]. No multiple subpial transection (MST) was performed in these cases. Because there was usually an initial early response to MSTs for epileptogenic zone over the rolandic cortex, the results were not durable, and seizure outcomes were less than satisfactory over time

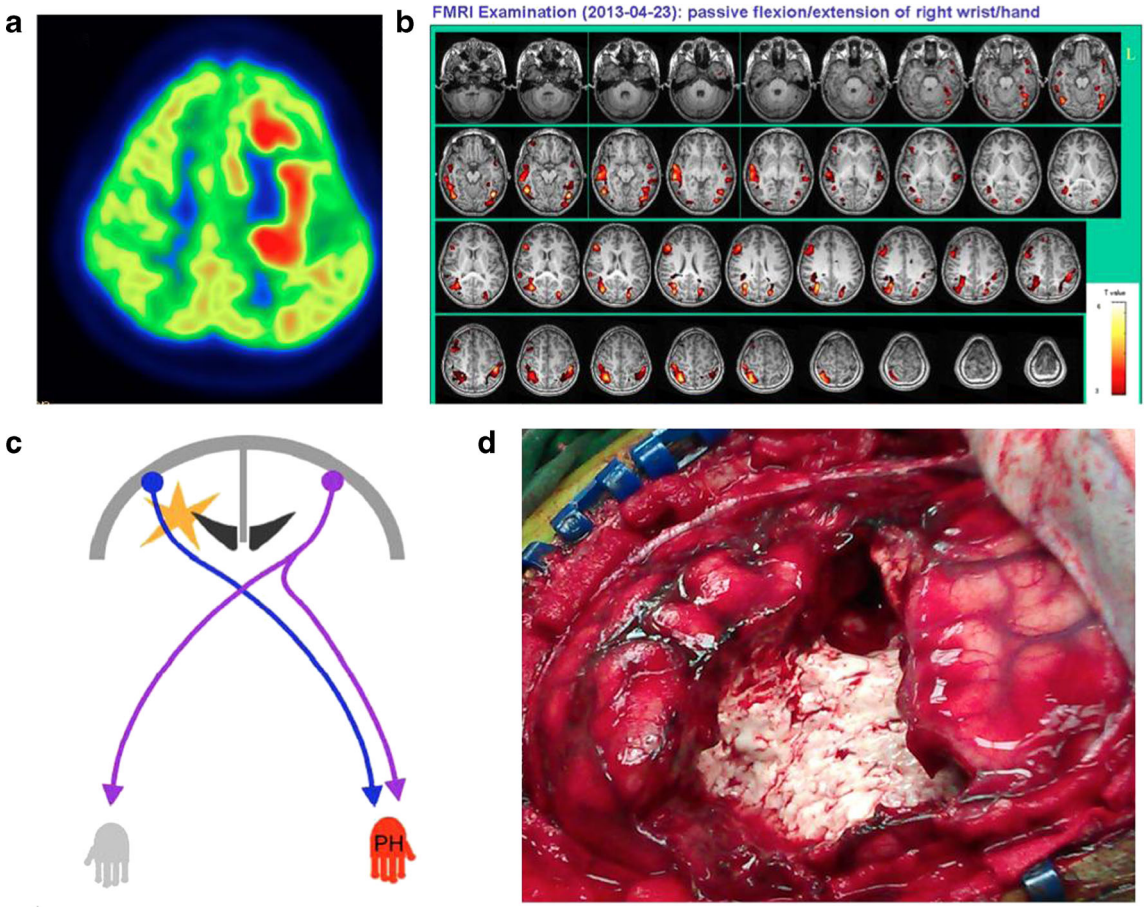

Fig. 3 A 9-year-old boy with right hemiparesis and mental retardation before surgery and ictal FDG-PET showed hypermetabolism over left rolandic area (**a**). Functional MRI demonstrated passive motor tasks of right hand/wrist in bilateral motor cortex (**b**). Response of the right limbs to transcranial stimulation (TCS) over the lesioned hemisphere and bilateral muscle response to TCS over the unaffected hemisphere indicating a bilateral corticospinal projection. *PH* paretic hand, *right side* (**c**). Complete resection of FCD type IIa in the rolandic area (**d**)

[36–38]. Complete resection of FCD in children is not a necessarily compensated neurological function as trade-off.

The only type IIId case demonstrated FCD with Rasmussen's encephalitis. We tried to resect the FCD part correlated to ictal PET hot area instead of hemispherectomy for treatment of his epilepsia partialis continua, but the result was Engel class III. The other two temporal type III cases all achieved seizure freedom due to complete resection. Therefore, the seizure outcome of type III should take the dual pathology in consideration together.

It is worth to mention that the FCD may be localized by EEG after corpus callosotomy and visible in MRI after myelination of the brain (older than 3 years old), which was demonstrated in one case of West syndrome in the current study [39, 40].

MEG and EEG appear to be complementary in recording interictal events. MEG is helpful and increases sensitivity to detect abnormal lesion on MRI, but MEG alone is not conclusive to define the exact area for surgical resection [23].

The seizure-free outcome in 72 % and Engel class II in further 6 % of our study is compatible with other case series in the literature [11–14]. There was no significant difference in seizure and cognitive outcomes between type I and type II FCD cases in current series.

Conclusions

For drug-resistant epilepsy with focality, earlier surgical intervention should be indicated. If severe functional impairment was already caused by early onset (<6 years/old) and long duration of seizure (>2 years), there is little chance of catch-up in neurological development that even become seizure-free. Complete resection is the single most important predictor of epilepsy outcome, and it needs multimodality approach and teamwork to achieve this goal. Early surgical intervention and complete resection of the lesion help for a better seizure control, cognitive function development, and quality of life. FCD is not uncommon to involve the rolandic area, and it is acceptable to resect it in children without significant sacrifice of neurological function. Further prospective longitudinal cohort studies on well-defined patient populations who are

treated surgically or medically at different times will be needed to clarify these multifactorial issues.

References

1. Taylor DC, Falconer MA, Bruton CJ, Corsellis JA (1971) Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry 34:369–387
2. Blumcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Ozkara C, Raybaud C, Represa A, Roper SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R (2011) The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia 52:158–174
3. Sisodiya SM, Fauser S, Cross JH, Thom M (2009) Focal cortical dysplasia type II: biological features and clinical perspectives. Lancet Neurol 8:830–843
4. Raymond AA, Fish DR, Sisodiya SM, Alsanjari N, Stevens JM, Shorvon SD (1995) Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumour and dysgenesis of the archicortex in epilepsy. Clinical, EEG and neuroimaging features in 100 adult patients. Brain : J Neurol 118(Pt 3):629–660
5. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, Cavalcanti D, Baulac M (1998) Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 51:1256–1262
6. Barkovich AJ, Kuzniecky RI, Bollen AW, Grant PE (1997) Focal transmantle dysplasia: a specific malformation of cortical development. Neurology 49:1148–1152
7. Bastos AC, Comeau RM, Andermann F, Melanson D, Cendes F, Dubeau F, Fontaine S, Tampieri D, Olivier A (1999) Diagnosis of subtle focal dysplastic lesions: curvilinear reformatting from three-dimensional magnetic resonance imaging. Ann Neurol 46:88–94
8. Chan S, Chin SS, Nordli DR, Goodman RR, DeLaPaz RL, Pedley TA (1998) Prospective magnetic resonance imaging identification of focal cortical dysplasia, including the non-balloon cell subtype. Ann Neurol 44:749–757
9. Hirabayashi S, Binnie CD, Janota I, Polkey CE (1993) Surgical treatment of epilepsy due to cortical dysplasia: clinical and EEG findings. J Neurol Neurosurg Psychiatry 56:765–770
10. Keene DL, Jimenez CC, Ventureyra E (1998) Cortical microdysplasia and surgical outcome in refractory epilepsy of childhood. Pediatr Neurosurg 29:69–72
11. Hong SC, Kang KS, Seo DW, Hong SB, Lee M, Nam DH, Lee JI, Kim JS, Shin HJ, Park K, Eoh W, Suh YL, Kim JH (2000) Surgical treatment of intractable epilepsy accompanying cortical dysplasia. J Neurosurg 93:766–773
12. Hader WJ, Mackay M, Otsubo H, Chitoku S, Weiss S, Becker L, Snead OC 3rd, Rutka JT (2004) Cortical dysplastic lesions in children with intractable epilepsy: role of complete resection. J Neurosurg 100:110–117
13. Cohen-Gadol AA, Ozduman K, Bronen RA, Kim JH, Spencer DD (2004) Long-term outcome after epilepsy surgery for focal cortical dysplasia. J Neurosurg 101:55–65
14. Kral T, Clusmann H, Blumcke I, Fimmers R, Ostertun B, Kurthen M, Schramm J (2003) Outcome of epilepsy surgery in focal cortical dysplasia. J Neurol Neurosurg Psychiatry 74:183–188
15. Wyllie E, Comair YG, Kotagal P, Raja S, Ruggieri P (1996) Epilepsy surgery in infants. Epilepsia 37:625–637
16. Vasconcellos E, Wyllie E, Sullivan S, Stanford L, Bulacio J, Kotagal P, Bingaman W (2001) Mental retardation in pediatric candidates for epilepsy surgery: the role of early seizure onset. Epilepsia 42:268–274
17. Freitag H, Tuxhorn I (2005) Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 46:561–567
18. Battaglia D, Rando T, Deodato F, Bruccini G, Baglio G, Frisone MF, Panto T, Tortorella G, Guzzetta F (1999) Epileptic disorders with onset in the first year of life: neurological and cognitive outcome. Eur J Paediatr Neurol : EJPN : Off J Eur Paediatr Neurol Soc 3:95–103
19. Hermann B, Seidenberg M, Bell B, Rutecki P, Sheth R, Ruggles K, Wendt G, O'Leary D, Magnotta V (2002) The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. Epilepsia 43:1062–1071
20. Muter V, Taylor S, Vargha-Khadem F (1997) A longitudinal study of early intellectual development in hemiplegic children. Neuropsychologia 35:289–298
21. Smith ML, Elliott IM, Lach L (2002) Cognitive skills in children with intractable epilepsy: comparison of surgical and nonsurgical candidates. Epilepsia 43:631–637
22. Engel Jr J (1993) Outcome with respect to epileptic seizures. Surgical treatment of the epilepsies: 609-621
23. Otsubo H, Ochi A, Elliott I, Chuang SH, Rutka JT, Jay V, Aung M, Sobel DF, Snead OC (2001) MEG predicts epileptic zone in lesional extrahippocampal epilepsy: 12 pediatric surgery cases. Epilepsia 42:1523–1530
24. Phi JH, Cho BK, Wang KC, Lee JY, Hwang YS, Kim KJ, Chae JH, Kim IO, Park SH, Kim SK (2010) Longitudinal analyses of the surgical outcomes of pediatric epilepsy patients with focal cortical dysplasia. J Neurosurg Pediatr 6:49–56
25. Edwards JC, Wyllie E, Ruggeri PM, Bingaman W, Luders H, Kotagal P, Dinner DS, Morris HH, Prayson RA, Comair YG (2000) Seizure outcome after surgery for epilepsy due to malformation of cortical development. Neurology 55:1110–1114
26. Bjornaes H, Stabell K, Henriksen O, Loyning Y (2001) The effects of refractory epilepsy on intellectual functioning in children and adults. A longitudinal study. Seizure : J Br Epilepsy Assoc 10:250–259
27. Neyens LG, Aldenkamp AP, Meinardi HM (1999) Prospective follow-up of intellectual development in children with a recent onset of epilepsy. Epilepsy Res 34:85–90
28. Harris JC (1998) Developmental neuropsychiatry: assessment, diagnosis, and treatment of developmental disorders. Oxford University Press
29. Elger CE, Helmstaedter C, Kurthen M (2004) Chronic epilepsy and cognition. Lancet Neurol 3:663–672
30. Luton LM, Burns TG, DeFilippis N (2010) Frontal lobe epilepsy in children and adolescents: a preliminary neuropsychological assessment of executive function. Arch Clin Neuropsychol : Off J Nat'l Acad Neuropsychologists 25:762–770
31. Weaver KE, Chaovalitwongse WA, Novotny EJ, Poliakov A, Grabowski TG, Ojemann JG (2013) Local functional connectivity as a pre-surgical tool for seizure focus identification in non-lesion, focal epilepsy. Front Neurol 4:43
32. Stufflebeam SM, Liu H, Sepulcre J, Tanaka N, Buckner RL, Madsen JR (2011) Localization of focal epileptic discharges using functional connectivity magnetic resonance imaging. J Neurosurg 114:1693–1697
33. Pondal-Sordo M, Diosy D, Tellez-Zenteno JF, Girvin JP, Wiebe S (2006) Epilepsy surgery involving the sensory-motor cortex. Brain : J Neurol 129:3307–3314
34. Benifla M, Sala F Jr, Jane J, Otsubo H, Ochi A, Drake J, Weiss S, Donner E, Fujimoto A, Holowka S, Widjaja E, Snead OC 3rd, Smith ML, Tamber MS, Rutka JT (2009) Neurosurgical management of

intractable rolandic epilepsy in children: role of resection in eloquent cortex. Clin Article J Neurosurg Pediatr 4:199–216
35. Behdad A, Limbrick DD Jr, Bertrand ME, Smyth MD (2009) Epilepsy surgery in children with seizures arising from the rolandic cortex. Epilepsia 50:1450–1461
36. Blount JP, Langburt W, Otsubo H, Chitoku S, Ochi A, Weiss S, Snead OC, Rutka JT (2004) Multiple subpial transections in the treatment of pediatric epilepsy. J Neurosurg 100:118–124
37. Schramm J, Aliashkevich AF, Grunwald T (2002) Multiple subpial transections: outcome and complications in 20 patients who did not undergo resection. J Neurosurg 97:39–47
38. Spencer SS, Schramm J, Wyler A, O'Connor M, Orbach D, Krauss G, Sperling M, Devinsky O, Elger C, Lesser R, Mulligan L, Westerveld M (2002) Multiple subpial transection for intractable partial epilepsy: an international meta-analysis. Epilepsia 43:141–145
39. Hur YJ, Kang HC, Kim DS, Choi SR, Kim HD, Lee JS (2011) Uncovered primary seizure foci in Lennox-Gastaut syndrome after corpus callosotomy. Brain Dev 33:672–677
40. Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, Vezina LG, Ilae CNSP (2009) Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia 50:2147–2153