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Comparison of MRI features and surgical outcome among the subtypes of focal cortical dysplasia

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ABSTRACT

Purpose: Focal cortical dysplasia (FCD) is the most common pathological diagnosis in patients who have undergone surgical treatment for intractable neocortical epilepsy. However, presurgical identification of MRI abnormalities in FCD patients remains difficult, and there are no highly sensitive imaging parameters available that can reliably differentiate among FCD subtypes. The purpose of our study was to investigate the surgical outcome in FCD patients with identifiable MRI abnormalities and to evaluate the prognostic role of the various MRI features and the characteristics of FCD pathology.
Methods: We retrospectively recruited epilepsy patients who had undergone surgical treatment for refractory epilepsy with focal MRI abnormalities and the pathological diagnosis of FCD. We evaluated the surgical outcome according to the pathological subtypes, and studied the prognostic roles of various MRI features. We used recently proposed three-tiered FCD classification system which included FCD type III when FCD occurs in association with other potentially epileptogenic pathologies.
Results: A total of 69 patients were included, and 68.1% of patients became seizure free. Patients with FCD type III had a lower chance for achieving seizure freedom (7/15) than in patients with isolated FCD (FCD types I and II) (40/54, $p = 0.044$). Cortical thickness and blurring of gray–white matter junction were more common in isolated FCD than in FCD type III, but most MRI features failed to differentiate between FCD types I and II, and only the transmantle sign was specific for FCD type II. We failed to find a prognostic value of specific MRI abnormalities of prognostic value in terms of post-epilepsy surgery outcome in FCD patients.
Conclusions: Our study showed that patients with FCD III have poor surgical outcome. Typical MRI features of isolated FCD such as cortical thickness and blurring of gray–white matter junction were less common in FCD type III and only transmantle sign was helpful in differentiating between FCD types I and II.

1. Introduction

Surgical resection has been an important alternative treatment for patients with intractable epilepsy. Although the EEG has an essential role in the diagnosis and prediction of outcome in epilepsy surgery, surgical outcome in patients without identifiable lesion on presurgical MRI is less satisfactory than in patients with MRI abnormalities, even with the precise focus localization on both scalp and even invasive EEG monitoring.[1,2] While the functional neuroimagings such as positron emission tomography (PET) and single photon emission CT (SPECT) can improve the sensitivity of detection of epileptogenic lesions, MRI is generally the imaging technique of choice for identifying the structural basis of the epilepsy.[3–5] It may be difficult to compare MRI with other diagnostic modalities, but it is clear that the localization of a lesion by MRI can both enhance confidence and provide more information than do PET or ictal SPECT, particularly when the localization is supported by an electrophysiologic study.[6]

Focal cortical dysplasia (FCD) is the most common pathological diagnosis in patients who underwent surgical treatment for intractable neocortical epilepsy.[7] Although the MRI characteristics of FCD are a very important component of the clinical assessment,[8–10] the presurgical identification of MRI abnormalities in FCD patients remains difficult, and there are no highly sensitive

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imaging parameters available that can reliably differentiate among FCD subtypes. Furthermore, MRI frequently does not show any abnormalities in patients with pathologically proven FCD,[11] and even in the presence of FCD, removal of the visual lesion along frequently does not lead to a seizure free outcome, implicating that the epileptogenic zone may extend beyond what can be visualized with the current structural imaging modalities.

While a broad spectrum of histopathology can be found in association with FCD,[12–15] previous studies have focused on describing the characteristics and surgical outcomes in patients with isolated FCD,[8,9,16,17] thus the surgical outcome and MRI features in FCD with other epileptogenic pathologies are less well documented. Recently, a new three-tiered classification of FCD was proposed by the International League Against Epilepsy (ILAE).[10] In this new classification, the definition of FCD types I and II is similar with the previous ones, referring to the isolated FCDs that are not adjacent to or associated with any other lesion. A novel FCD type III refers to those variants with cortical dyslamination that are adjacent to or associated with other potentially epileptogenic lesions. The purpose of our study was to investigate the surgical outcome in FCD patients with identifiable MRI abnormalities according to the new ILAE classification of FCD, and to evaluate the prognostic role of various MRI features and the characteristics of FCD pathology.

2. Methods

2.1. Patients

Our study included consecutive patients who had undergone surgical treatment for refractory epilepsy, had presurgical MRI abnormalities, and was confirmed with pathological diagnosis of FCD at the Seoul National University Hospital between November 1995 and June 2009. All patients had intractable epilepsy, despite taking the appropriate anticonvulsant drugs. We only included patients who underwent focal resection and excluded patients with functional hemispherectomy or corpus callosotomy. Surgical outcome was divided into seizure free and not seizure free.

2.2. Sequence of brain MRI and interpretation

All patients underwent brain MRI. Standard MRI was performed on either a 1.5-T or a 3.0-T unit (Signa Advantages, General Electric Medical Systems, Milwaukee, WI), with conventional spin-echo T1-weighted sagittal and T2-weighted axial and coronal sequences in all patients. The section thickness and the conventional image gaps were 5 mm and 1 mm. T1-weighted 3D magnetization-prepared rapid acquisition of gradient-echo sequences with 1.5 mm thick sections of the whole brain and T2-weighted fluid-attenuated inversion recovery (FLAIR) images of 3 mm thick sections were also obtained in the oblique coronal plane of the temporal lobe. The angle of oblique coronal imaging was perpendicular to the long axis of the hippocampus. Spatial resolution was approximately 1.0 mm $\times$ 1.0 mm (matrix, 256 mm $\times$ 256 mm; field of view, 25 cm).

We excluded patients from the study when the MRI was performed on a 1.0-T unit or it did not follow our MRI protocol for epilepsy for decreased sensitivity. In particular, we analyzed the frequency of several commonly documented MRI abnormalities in FCD patients and studied their prognostic implications. The MRI abnormalities included increased cortical thickness, blurring of the gray–white matter junction, increased cortical or subcortical signal on the T2-weighted of FLAIR images, a radially oriented linear or conical transmantle stripe of T2 hyperintensity (transmantle sign), and localized cortical thinning or atrophy. Additionally, we studied the presence of other MRI findings such as mass or cyst-like appearance because these MRI findings were previously observed in pathologically confirmed FCD patients, and occasionally found in our surgical series of FCD.[18,19]

2.3. Video-EEG monitoring and functional neuroimaging

Interictal and ictal scalp EEGs were recorded in all patients using a video-EEG monitoring system, with electrodes placed according to the international 10–20 system, along with additional anterior temporal electrodes. In patients for whom other methods gave inconclusive or discordant results, we used a combination of grids and strips for intracranial EEG. Grid and strip placements were determined by the results of presurgical evaluations. At least three habitual seizures were recorded during scalp and intracranial EEG monitoring. When necessary, preoperative and intraoperative functional mapping and intraoperative electrocorticography were also performed.

^{18}F-fluorodeoxyglucose PET was performed during the interictal period (no seizures for more than 24 h) and ictal SPECT was performed during video-EEG monitoring. The detailed methods of functional neuroimaging were described previously.[6]

2.4. Surgery and pathology

The surgical area was decided based on the clinical, neuroimaging, and electrophysiological results. In our center, the resection margin for epilepsy of neocortical origin with MRI abnormalities was defined by (A) the presence of either a discrete lesion on MRI with compatible ictal EEG; and (B) the absence of eloquent cortex.

Pathological findings were classified according to the new ILAE FCD classification system. The new ILAE classification for FCD expands the Palmini classification scheme with the addition of a new type of FCD associated with a principal epileptogenic lesion. In this system, FCD type I referred to isolated lesions of the cerebral cortex, which presents as being either radial (FCD IA), tangential (IB), or radial and tangential dyslamination (IC). FCD type II referred to isolated lesions characterized by cortical dyslamination and dysmorphic neurons without (FCD IIA) or with balloon cells (IIB). FCD type III was defined when FCD occurred in combination with hippocampal sclerosis (HS) (FCD IIIA), with epilepsy associated tumors (IIIB), with vascular malformation (IIIC), and with epileptogenic lesions acquired in early life such as traumatic injury, ischemic injury or encephalitis (IIID). Mild malformation of cortical development (mMCD) referred to pathologically mild malformation involving hypercellularity in or outside layer I.

We excluded patients who had pathological evidence of brain tumors in addition to FCD (FCD IIIB), due to the frequent overlap between the pathology of several tumors and FCD, and the limited amount of tissue available for assessment in some patients.[20] Furthermore, brain tumors themselves have characteristic MRI findings and strong epileptogenecity, while our study aimed to investigate the MRI features and surgical outcomes according to the pathological subtypes in FCD patients.[21,22]

2.5. Statistical tests

We compared the demographic data of the seizure free group with the non-seizure free group and the clinical implications of MRI features using the Student's *t*-test or the Mann–Whitney *U* test for continuous variables, and with a chi-square or Fisher's exact test for categorical variables.

All analyses were conducted using SPSS version 12.0 (SPSS Inc., Chicago, IL) and STATA version 9.2 (STATA Corp., College Station, TX). $p < 0.05$ was considered significant.

3. Results

3.1. Patients and surgical outcome

A total of 69 patients were included for the present study. The subjects consisted of 46 men and 23 women, and the mean age of the patients at the time of surgery was 34.6 (±9.9) years (range 17–55 years). Of the patients, 23 had frontal lobe epilepsy, 24 had neocortical temporal lobe epilepsy, seven had parietal lobe epilepsy, five had occipital lobe epilepsy, and 10 had multifocal epilepsy. The proportion of seizure free patients was 66.7% (46/69) during the follow-up for more than 2 years, whereas 33.3% (23/69) of patients did not become seizure free.

3.2. Frequency of MRI abnormalities according to the pathological subtypes of FCD

The most frequent MRI abnormalities were blurring of the gray–white matter junction and cortical T2/FLAIR high signal intensity, which were found in 33 patients (47.8%). Cortical thinning or atrophy was found in 26 patients (37.7%), increased cortical thickness was found in 32 patients (30.4%), and subcortical T2/FLAIR high signal intensity was found in 12 patients (17.4%) including 4 patients with the features of a transmantle sign (5.8%). Eleven patients (15.9%) showed MRI abnormalities with mas or cyst-like appearance, most commonly in the mesial temporal areas (Fig. 1). Interestingly, increased cortical thickness and blurring of the gray–white matter junction frequently occurred together, and these combined MRI features were predictive of FCD IIB. We failed to find a prognostic value of specific MRI abnormalities on the surgical outcome in FCD patients (Table 1), but complete resection of MRI abnormalities was associated with the seizure free outcome ($p = 0.05$). PET and ictal SPECT were performed in 60 and 44 patients, respectively. The results of PET and ictal SEPCT and the proportion of complete resection of MRI lesion were also presented in Table 1.

3.3. Surgical outcome in different pathologic subtypes of FCD

Pathologically, 15 patients showed characteristics of FCD IA, 15 patients of FCD 1B, 9 patients of FCD IIA, 11 patients of FCD IIB, 6 patients of FCD IIIA, 3 patients of FCD IIIC, and 6 patients of FCD IIID. We excluded patients with FCD IIIB from the study, and no patient showed pathological characteristics of mMCD and FCD IC.

Excluding patients with adjacent epileptogenic pathology (FCD type III), patients were divided into those with mild pathology (FCD IA, and FCD IB) and those with severe pathology (FCD IIA, and IIB). There was no difference in the surgical outcome between the two groups (20/30 vs 20/24. $p = 0.22$), and the frequency of specific MRI features was similar between the two groups, except for the transmantle sign, which is well documented as being specific for FCD II. When patients were divided into those with isolated pathology (FCD types I and II) and those with adjacent pathology (FCD type III), patients in the isolated pathology group had a greater chance of becoming seizure free than did patients with adjacent pathology group (14/54 vs 7/15, $p = 0.044$). Some

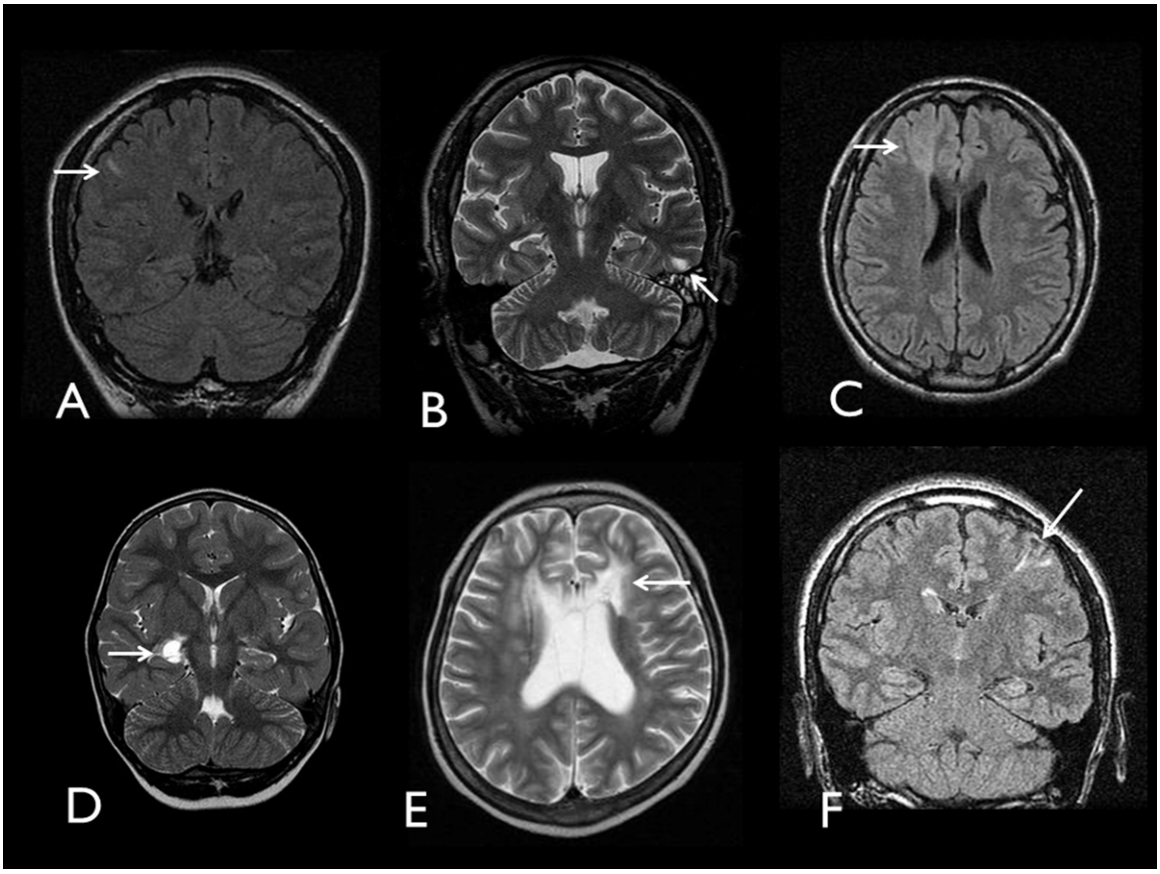

Fig. 1. Illustrative MRI features in FCD patients. (A) Cortical high signal intensity on the FLAIR image in a patient with FCD IA; (B) mass-like lesion on the T2-weighted image in a patient with FCD IB; (C) cortical thickness, blurring of the gray–white matter junction, and subcortical high signal intensity (transmantle sign) on the FLAIR image in a patient with FCD IIB; (D) cyst-like lesion on the T2-weighted image in a patient with FCD IIIA (FCD with hippocampal sclerosis); (E) subcortical high signal intensity lesion on the T2-weighted image in a patient with FCD IIIC (FCD with angiomatosis); (F) cortical high signal intensity, cortical atrophy, and trauma-related scar on the FLAIR image in a patient with FCD IIID (FCD with traumatic lesion) FCD: focal cortical dysplasia, FLAIR: fluid-attenuated inversion recovery.

Table 1
Frequency of MRI abnormalities according to the pathological subtypes of FCD based on the new ILAE classification.

	Increased cortical thickness	Blurring of gray–white matter junction	Increased cortical thickness with blurring of gray–white matter junction	Increased cortical signal intensity	Increased subcortical signal intensity	Mass or cyst-like appearance	Cortical atrophy	Transmantle sign	PET ($N=60$)	SPECT ($N=44$)	Complete Resection	Seizure free outcome
FCD IA (15)	2 (13.3%)	7 (46.7%)	2 (13.3%)	7(46.7%)	4 (26.7%)	2 (13.3%)	8 (53.3%)	0 (0%)	11/14	5/9	10 (66.7%)	9 (60.0%)
IB (15)	7 (46.7%)	7(46.7%)	6 (40.0%)	7(46.7%)	1 (6.7%)	3 (20.0%)	5 (33.3%)	0 (0%)	10/12	3/8	9 (60%)	11 (73.3%)
IIA (10)	1 (10.0%)	3 (30.0%)	0 (0%)	3 (30.0%)	1 (10.0%)	3 (30.0%)	5 (50.0%)	1 (10.0%)	6/9	5/7	8 (80%)	9 (90.0%)
IIB (14)	11 (78.6%)	13 (92.9%)	11 (78.6%)	8 (57.1%)	5 (35.7%)	0 (0%)	0(0%)	3 (21.4%)	12/12	9/11	11 (78.6%)	11 (78.6%)
IIIA (6)	0 (0%)	1 (16.7%)	0 (0%)	3 (50.0%)	0 (0%)	2 (33.3%)	3 (50.0%)	0 (0%)	4/4	3/3	3 (50%)	2 (33.3%)
IIIC (3)	0 (0%)	1 (33.3%)	0 (0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0%)	2/3	1/1	2 (66.7%)	1 (33.3%)
IIID (6)	0 (0%)	1 (16.7%)	0 (0%)	4 (66.7%)	0 (0%)	0 (0%)	4 (66.7%)	0 (0%)	6/6	1/5	3 (50%)	4 (66.6%)
Total (69)	21 (30.4%)	33 (47.8%)	19 (27.5%)	33 (47.8%)	12 (17.4%)	11 (15.9%)	26 (37.7%)	4 (5.8%)	51/60	27/44	46 (66.7%)	47 (68.1%)
PET (60)	14/17	24/29		26/29	10/11	8/10	19/22	4/4				
SPECT (44)	9/13	16/24		14/25	6/9	2/2	11/21	4/4				
Complete resection	15/21	23/33		20/33	7/12	8/11	13/26	4/4				
Seizure free Outcome	16/21 ($p=0.34$)	22/33 ($p=0.81$)	14/19 ($p=0.54$)	24/33 ($p=0.43$)	8/12 ($p=0.91$)	6/11 ($p=0.29$)	16/26 ($p=0.36$)	3/4 ($p=1.00$)		35/46 ($p=0.05$)		

ILAE, International League Against Epilepsy; FCD, focal cortical dysplasia; PET, positron emission tomography; SPECT, single photon emission CT.

FCD-specific MRI features, including increased cortical thickness and blurring of the gray–white matter junction, were less frequent in patients with FCD type III. One interesting finding is that cortical thinning or atrophy was more frequent in FCD patients with adjacent pathology than with isolated pathology and in the isolated pathology group, it was more frequent in patients with FCD type I than with FCD type II, although it did not reach statistical significance (Table 2).

4. Discussion

Forty-seven (68.1%) of 69 patients became seizure free after surgical resection. The seizure free rate was better than those in our previous studies with isolated FCD or FCD accompanied by HS as dual pathology.[6,23] This result can be explained by the inclusion of patients with identifiable MRI lesions, because the presence of MRI abnormality is an important prognostic factor of epilepsy surgery in FCD patients. A previous study observed that the appearance of the blurring the gray–white matter junction was associated with favorable surgical outcome,[17] however, we could not confirm this result. Even the transmantle sign, which is specific for FCD type II,[8,24–26] was not a predictor of a favorable surgical outcome. This result may be related to the limited number of patients because the positive prognostic effect of severe pathological features has been documented in previous studies including our study.[6,26,27] One interesting finding in our study was the poorer surgical outcome in patients with FCD type III than with isolated FCD (FCD types I and II). The difference in prognosis can mostly be attributable to the disappointingly low chance of seizure free outcome in FCD type III. However, it is hard to evaluate the clinical implication of our results because we included only 15 patients with FCD type III, the surgical outcome would be variable among the subtypes of FCD type III, and there are only limited studies on the surgical outcome in FCD III patients.[17,28]

A previous study documented that increased cortical thickness and gray matter signal abnormality were more common in FCD type II.[8] Our study found that increased cortical thickness and blurring of the gray–white matter junction were relatively common findings in FCD type II. In parallel with previous studies, the transmantle sign was encountered exclusively in FCD type II patients,[8,24–26] However, with the low incidence of the transmantle sign, we failed to identify reliable MRI features which could be helpful in differentiating between FCD types I and II. On the other hand, there was a marked difference in the MRI features between the isolated FCD and FCD type III. While cortical thinning or atrophy was a relative common MRI finding in FCD type III, increased cortical thickness and blurring of gray–white matter junction were remarkably rare findings in FCD type III, although these MRI features have been considered as typical for FCD. Interestingly, cortical thinning or atrophy was a frequent MRI finding in one study with FCD patients with a history of prenatal and perinatal injury.[29] Since the study was performed before the introduction of new ILAE classification for FCD, the pathological degree was graded as mMCD or FCD type I. However, it is probable that most patients with prenatal and perinatal brain injury can be re-classified as FCD type III with new ILAE classification, and moreover, the observation would be consistent with our results stating that cortical thinning or atrophy is a common MRI finding in FCD type III. Another interesting finding in our study is the presence of mass or cyst-like lesions in FCD patients. The mass or cyst-like lesions on MRI have a prediction for the mesial temporal areas, but we could not find the reason of this prediction for mesial temporal areas. The MRI features in this group can be described as cortical thickness or increased cortical or subcortical signal intensity, but we think that this MRI feature is worth documenting separately as another MRI feature in FCD patients, because the

Table 2
Demographic features, surgical outcomes and the frequency of MRI abnormalities according to the subgroups of FCD.

	FCD I ($N=30$)	FCD II ($N=24$)	p-Value	Isolated FCD (FCD I and II) ($N=15$)	FCD III ($N=54$)	p-Value
Age at operation	29.0 ± 14.2	25.5 ± 14.2	0.80	27.5 ± 14.1	36.5 ± 9.8	0.023
Male	18	15	0.85	33	13	0.07
Increased cortical thickness	9	12	0.13	21	0	0.003
Blurring of gray–white matter junction	14	16	0.14	30	3	0.02
Increased cortical signal intensity	14	11	0.95	25	8	0.63
Increased subcortical signal intensity	5	6	0.45	11	1	0.44
Mass or cyst-like appearance	5	3	0.72	8	3	0.69
Cortical atrophy	13	5	0.08	18	8	0.15
Transmantle sign	0	4	0.03	4	0	0.57
Seizure free outcome	20	20	0.22	40	7	0.044

FCD, focal cortical dysplasia; *N*, number of patients.

clinical features and MRI findings were largely indistinguishable from those of benign brain tumors.[19,21,30] Although we did not exclude patients with mMCD pathology, there was no patient with mMCD pathology with the corresponding MRI abnormality. Due to the fact that mMCD is defined as a pathologically mild malformation involving hypercellularity in or outside layer I, these pathological features are reasonably not visible using the current MRI technique.

The pathological features of FCD type III are not quite different from the isolated FCD type I.[10] FCD IIIA is defined when the temporal cortex shows alternations in architectural organization or cytoarchitectural composition in combination with HS. This subtype does not include the dual pathology condition, which is when patients with HS have a second principal lesion affecting the brain, including FCD type II.[10] Although several reports have described the presence of dysplastic lesions in patients with HS as being associated with early seizure onset, high seizure frequency, and poor surgical outcomes,[31–33] the clinical implications of the dysplastic lesions in patients with HS are still controversial.[34,35] While FCD IIIC is defined when alterations in architectural or cytoarchitectural composition occur adjacent to various vascular malformations, there are only limited reports on the FCD IIIC,[36,37] with even fewer surgical cases.[38,39] Considering the strong epileptogenecity of some vascular malformations, the apparent architectural change may be acquired secondary to the development of the principal lesion.[10,40] FCD IIID refers to the altered architectural or cytoarchitectural composition of the neocortex, adjacent to other lesions acquired during early life. These lesions comprised a large spectrum, including traumatic brain injury, prenatal or perinatal vascular events and inflammatory or infectious diseases.[12,13,16,41,42] The re-organization of the cortical cytoarchitecture can also be acquired secondary to the development of other epileptogenic pathologies. Interestingly, the evidence of coexistent perinatal or perinatal injuries was frequently found in several pathological and clinical studies with a mild degree of FCD,[14,29] thus, it is possible that the prenatal or perinatal injuries may be a common cause of the development of FCD, particularly for the mild pathological degree including mMCD and FCD type I as well as FCD type III.

Our study suggests that the surgical outcome would be less favorable in FCD type III patients, and careful investigation should be considered in these patients. Typical MRI features of FCD types I and II, such as cortical thickness and blurring of the gray–white matter junction, were less common in FCD type III whereas cortical thinning or atrophy was relatively common in FCD type III. Most MRI features failed to differentiate between FCD types I and II, but only the transmantle sign was specific for FCD types II. However, since we studied only a limited number of patients, further studies are needed in order to completely understand the surgical outcome and MRI features in FCD patients.

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