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피질이형성증의 약물반응도와 관련된 자기공명영상 소견

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Prediction of Pharmacoresponsiveness in Focal Cortical Dysplasia with Magnetic Resonance Imaging

by

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ABSTRACT

Background: Focal cortical dysplasia (FCD) is a common cause of intractable epilepsy in children and adolescents. Clinical features vary broadly, including treatment response. The aim of this study was to identify specific magnetic resonance imaging (MRI) features that could be used to predict pharmacoresponsiveness in FCD patients.

Methods: We retrospectively reviewed brain MRI scans of 76 children and adolescents who had a lesion consistent with FCD, which correlated with focal onset epilepsy. Pharmacoresponsiveness was defined as a 2-year seizure-free period while receiving antiepileptic drugs. MRI features were compared between a pharmacoresponsive and pharmacoresistant group. Patients were categorized into 4 groups according to their MRI features, such as the severity of gray-white matter boarder blurring, lesion location, and signal changes on T2-weighted images. Clinical outcomes, including responses to the antiepileptic drugs were compared between these groups.

Results: Twenty-four patients (31.6%) responded well to the antiepileptic drugs, while 52 patients showed resistance. Localized signal changes were more frequently found in the pharmacoresponsive group in comparison to the pharmacoresistant group (70.8% vs. 38.5%, respectively, $p = 0.013$). In contrast, diffuse signal changes were more common among the patients with pharmacoresistance (25% vs. 8.3%,

respectively, p = 0.028). When FCD were categorized into 4 subtypes according to their MRI features, diffuse type with low/iso cortical signal intensities had an earlier age-of-onset and a lower full-scale IQ compared to other subtypes.

Conclusions: This study suggests that FCD patients may respond variously to antiepileptic medication. The extent of the lesion, distinguishable by signal changes, may be related to the pharmacoresponsiveness.

Keywords: malformations of cortical development, childen, magnetic resonance imaging, prognosis, antiepileptic drug

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List of abbreviations and symbols

FCD- Focal cortical dysplasia

CDT-Cortical dyspasia of Taylor

IQ-Intelligent quotient

AED-Antiepileptic drug

MRI- Magnetic resonance imaging

EEG-Electroencephalography

SI-Signal intensity

T2W-T2-weighted image

T1W-T1-weighted image

FLAIR-Fluid attenuated inversion recovery

Introduction

Focal cortical dysplasia (FCD) is a term widely used for a spectrum of localized regions of malformed cerebral cortex [1]. It has been consistently recognized as one the most common causes of drug-resistant epilepsy [2] and as many as 25–53% of patients undergoing surgery for intractable epilepsy are patients with FCD [3,4]. Recently, as more epilepsy surgeries are being performed, even more FCD lesions are being recognized, and it has become clear that FCD consists of a more heterogeneous population than previously believed [5]. In addition to isolated lesions, dysplastic lesions around other epileptogenic lesions are newly being recognized as FCD, and have been introduced as FCD subtype III [1].

With the heterogeneous nature of FCD, predicting outcomes based on histologic subtype has been difficult. Similarly, efforts to predict histologic subtypes before surgery have been unsuccessful [5]. No FCD subtype has been totally distinguished from other subtypes on the basis of unique magnetic resonance imaging (MRI) features or clinical outcomes. Various radiologic characteristics have been observed when using MRI scans to diagnose FCD subtypes, including apparently normal scans [6].

A new classification was proposed in 2011 by the International League against Epilepsy (ILAE) to address the above issues, but the

system remains based on histologic analysis [1]. Unfortunately, the quality of histologic analysis and evaluation of FCD lesions varies widely. Additionally, FCD subtypes such as FCD Ia can be distinguished only when the pathologists are conscious of the diagnosis before the tissue preparation. This suggests that the same lesion can have different diagnoses in different situations at different epilepsy centers. Indeed, inter- and intraobserver reproducibility of FCD type I cases have been reported to be as low as 50% [7]. Additionally, when patients with FCD receive surgery, 50% do not achieve complete seizure control. In these patients, resected and thus, histologically evaluated tissue may not contain or represent the whole epileptogenic or dysplastic tissue. Sometimes, the diagnosis changes after patients receive a second epilepsy surgery.

Recently, different approaches have been pursued in order to identify specific features that can predict outcomes without a consideration for subtypes. For example, in one study, MRI-negative patients were compared with MRI-positive patients [8]. Another study analyzed patients with a transmantle sign and reported an association between the transmantle sign and favorable seizure control after surgery, regardless of their subtypes [9]. More recently, independent MRI features and their combinations in FCD type II patients have been reviewed [10]. However, all of these studies remain focused on the

patients who underwent epilepsy surgery, thus excluding the patients with a more benign seizure outcome.

Brain MRI is the most common method and in many epilepsy centers, it is the only technique used to identify underlying lesions responsible for epilepsy [11]. With the advances in neuroimaging techniques along with the increasing use of high-resolution MRI scanners, even subtle epileptogenic lesions are now being recognized. Although FCD can only be definitively diagnosed histopathologically, MRI findings are increasingly being considered as diagnostically accurate for the identification of FCD lesions. According to a recent study, out of 118 patients who had pathologically proven FCD subtype II, 93 had abnormal MRI images. Of these, 97% were correctly identified as having dysplastic lesions, presurgically [12].

Transient pharmacoresponsiveness, defined as being seizure-free for more than 1 year while receiving antiepileptic drugs (AED), has been reported in 17% of patients with pathologically proven FCD [13]. However, in general, information regarding pharmacoresponsiveness is limited. The characteristics of the patients who would respond well to the medical therapy remain unknown. Predictive factors have not been determined.

The aim of this study was to identify specific magnetic resonance imaging (MRI) features that could be used to predict treatment

response including pharmacoresponsiveness in FCD patients.

Materials and Methods

Patient selection

One hundred and fifty-three subjects were obtained through the epilepsy and radiology database at the Seoul National University Children's Hospital (Seoul, South Korea) between January 2006 and March 2012; search terms used were "focal cortical dysplasia" and "epilepsy."

Only patients who met the following criteria were selected: (1) one identified ictal onset zone, correlated with a radiological lesion consistent with FCD as observed by MRI (2) focal epilepsy (at least two unprovoked seizures); (3) receiving AEDs; (4) ≤18 years of age. Ictal onset zones were determined by reviewing the patient's clinical history, their seizure semiology, EEG abnormalities, and other imaging modalities.

Patients were excluded if their EEG recordings detected more than one potential epileptogenic foci or if their MRI scans detected multiple lesions that could be ictal onset zones other than the lesion of interest. Patients were reviewed for hemimegalencephaly, neurofibromatosis, tuberous sclerosis, and tumors; patients suspected of having any of these disorders were excluded. Patients with a pathologic diagnosis of FCD, but with normal MRI scans, were not included. Similarly, patients with MRI scans consistent with FCD, but without a history of seizures,

were excluded.

Study design and data collection

Pharmacoresponsiveness was defined as being more than 2 years seizure-free while receiving AEDs. According to this definition, patients were classified as either drug-responsive or drug-resistant. Further classifications were based upon MRI findings. Pharmacoresponsiveness and other clinical outcomes were compared between both groups. Then, patients were categorized into 4 groups according to their MRI features as below. Clinical outcomes, including responses to the antiepileptic drugs were compared between these groups.

Data was collected by retrospectively reviewing their medical records. Information on the age-of-onset, sex, presence of mental retardation, intelligence quotient (IQ), duration of epilepsy, duration of treatment, duration of seizure freedom, history of surgery, brain pathology, and the location of the ictal onset zone were collected. MRI findings, EEG features, and the results of other imaging studies were also collected. Data on seizure frequency, presence of generalized tonic-clonic seizures, history of status epilepticus, and history of epilepsia partialis continua were also obtained.

MRI parameters

MRI scans were performed using a 1.5-Tesla unit MRI (Magnetom Avanto; Siemens, Erlangen, Germany or Signa; GE Medical Systems, Milwaukee, Wis) or a 3.0-Tesla MRI scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a standard head coil. The MRI protocol for epilepsy patients included axial (thickness: 4 mm) and oblique coronal (thickness: 3 mm) T2-weighted (T2W) sequences; oblique coronal (thickness: 3 mm) fluid-attenuated inversion recovery (FLAIR)-T2W sequences; and coronal (thickness: 2 mm), sagittal (thickness: 1 mm), and axial (thickness: 4 mm) T1-weighted (T1W) MPR/SPGR sequences. Axial (thickness: 5 mm) and coronal (thickness: 5 mm) post-gadolinium T1W sequences were also obtained.

MRI evaluation

First, signal abnormalities were screened on T2W and FLAIR images. Blurring/thickening of the gyrus and volume changes were then assessed on T1W-MPR/SPGR or T2W sequences, following which the whole images were reviewed. If a lesion appeared abnormal on one sequence, the area was also examined on other sequences. Transmantle sign was often identified on T2W or FLAIR sequences, but it was also checked on T1W sequences.

Radiologic diagnosis of FCD

A lesion was considered to be consistent with FCD only if FCD was the primary radiologic diagnosis given by 2 experienced pediatric neuroradiologists and 1 pediatric neurologist. The following features were assessed: (1) blurring of the gray-white matter junction; (2) cortical thickening; (3) volume changes, including focal atrophy; (4) signal changes in the cortex; (5) signal changes in the white matter; and (6) transmantle sign. These reviewers were aware of the diagnosis of epilepsy; however, they were not aware of the initial radiologic diagnosis, seizure semiology, EEG findings, or the subtype of FCD.

Radiologic classification of FCD

Patients were grouped into 4 categories according to their MRI features in the white matter, cortex, and the junctions between gray and white matter.

Severity of blurring between gray and white matter, mostly involving site and signal intensities (SI) on T2W images, was the factor primarily considered (Figure 1 and 2). Group 1 (White matter predominant type) had lesions located predominantly in the white matter, with severe white matter hyperintensity changes observed on T2W sequences; the margin between the cortex and white matter was usually discernible or slightly blurred. Group 2 (diffuse type) had diffuse lesions with a

severely blurred junction between the cortex and white matter; sometimes, the images in Group 2 displayed isointense or hypointense SI on T2W sequences. Group 3 (gray matter predominant type) had lesions located predominantly in the gray matter. Abnormal gyral shape or cortical thickening was the main feature, and the cortex-white matter junction was usually slightly blurred; sometimes, moderate cortex hyperintensities on T2W sequences were noted. Group 4 (extended gray matter type) was characterized by diffuse lesions that involved both gray and white matter. The junction between the cortex and white matter was usually moderately blurred; the cortex was often severely involved, depicting a similar appearance to group 3. Sometimes moderate cortex/white matter hyperintensites on T2W sequences were noted.

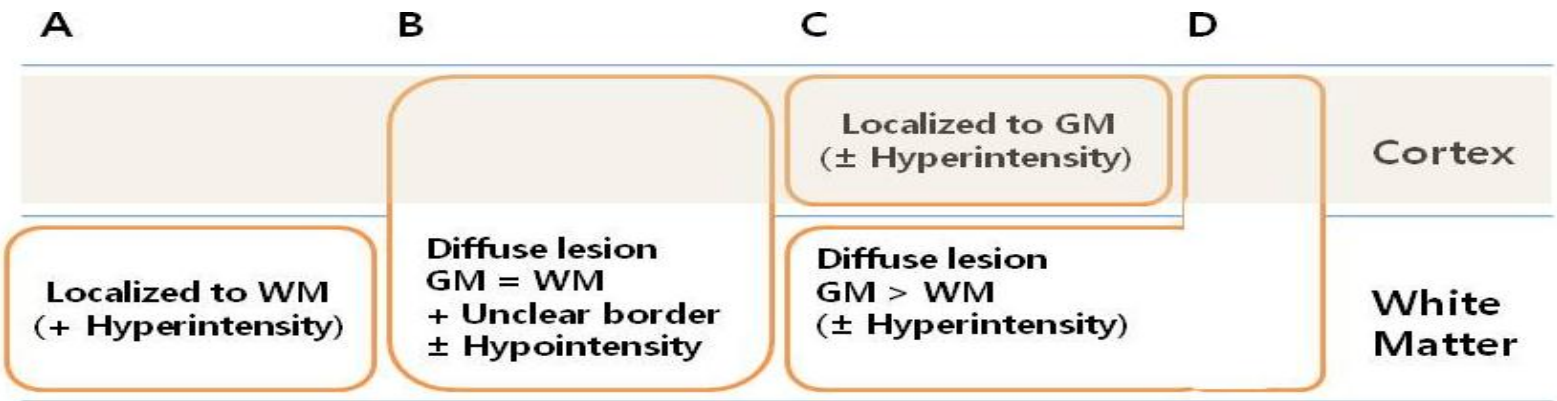

Figure 1. Radiologic classification of FCD. Images were classified into 4 subtypes according to the severity of blurring between gray and white matter, mostly involving site and signal intensities (SI) on T2-weighted (T2W) images. (A) White matter predominant type. Lesions located predominantly in the white matter with severe white matter hyperintense signal changes observed on T2W sequences. (B) Diffuse type. Diffuse lesions with a severely blurred junction between the cortex and white matter. Occasional isointense or hypointense SI on T2W sequences were noted. (C) Gray matter predominant type. Lesions located predominantly in the gray matter. (D) Extended gray matter type. Diffuse lesions that involved both gray and white matter. Abnormal gyral shape or cortical thickening was the main feature in this group. (GM, gray matter; WM, white matter)

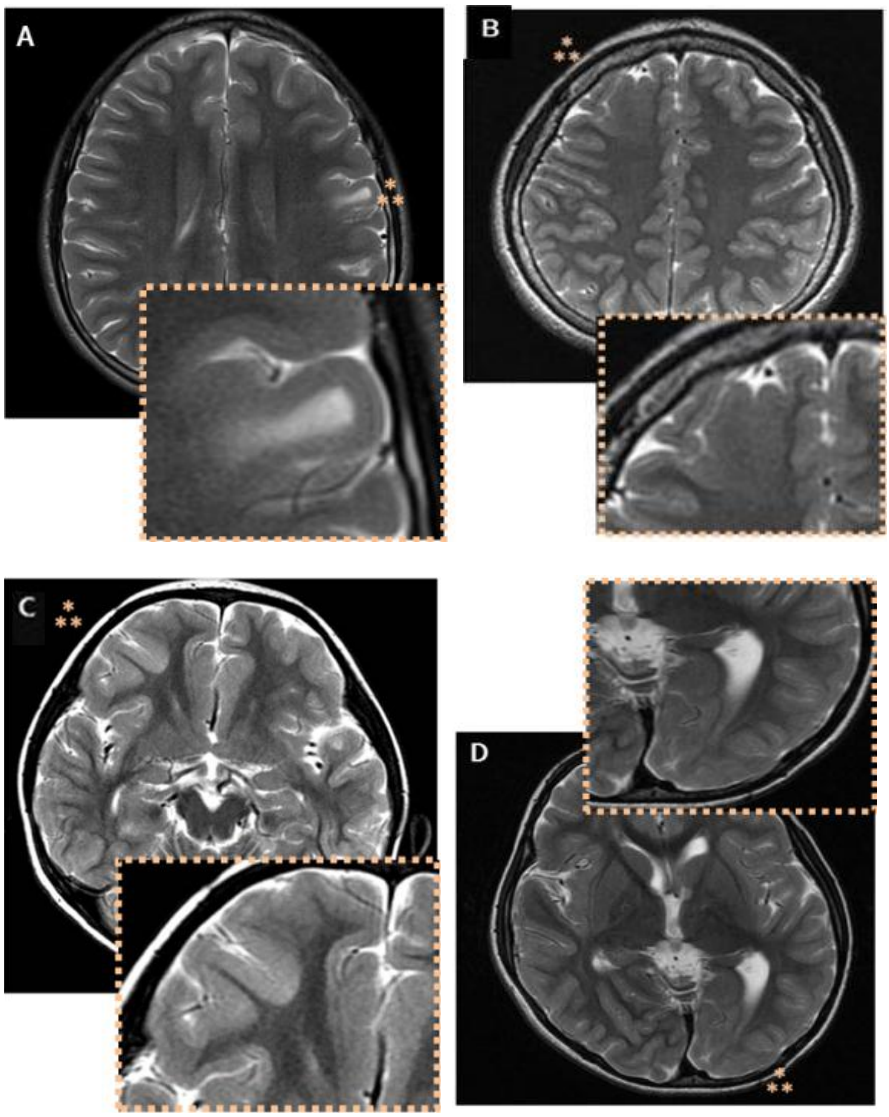

Figure 2. Images of 4 subtypes. (A) White matter predominant type; (B) Diffuse type with a severely blurred junction between gray and white matter; (C) Gray matter predominant type; (D) Extended gray matter type. Asterisk: a lesion consistent with focal cortical dysplasia. Inset (dashed line): magnified images of the lesion (asterisk).

Statistical analysis

Student *t*-tests or Mann-Whitney U tests were used to statistically compare different clinical continuous variables, including age of onset, IQ, duration for epilepsy/treatment, between the pharmacoresponsive and pharmacoresistant groups. Chi-square tests or Fisher's exacts test were used to assess differences in sex, mental retardation, surgery, and MRI features between these groups. ANOVA was used to evaluate the relationship between clinical outcomes and the FCD MRI subtypes. All continuous values were expressed as mean ± standard deviation (SD) or as median with reference range. Only P-values less than 0.05 were considered statistically significant. Analyses were carried out using SPSS software 19.0 for Windows (SPSS, Chicago, IL, U.S.A.).

Results

Patient characteristics

Seventy-six patients were included. Twenty-four patients (31.6%) experienced pharmacoresponsiveness, whereas 52 patients (68.4%) were pharmacoresistant throughout the study. Surgery was performed on 24 patients (31.6%), which resulted in a diagnosis of FCD type I in 8 (28.5%), FCD type IIa in 6 (21.4%) and FCD type IIb in 10 (35.7%). There were no significant between-group differences with regards to sex, location of the lesion, full-scale IQ, duration of epilepsy, and duration of treatment. The pharmacoresistant group had an earlier age-of-onset (4.05 ± 0.57 years) compared to the pharmacoresponsive group (5.90 ± 0.98 years); however, this was not statistically significant ($p = 0.094$). Details of these results are given in Table 1.

MRI findings in the pharmacoresponsive group and the pharmacoresistant group

Among 76, fourteen patients (18.4%) displayed volume changes, as observed by MRI. Twenty-seven patients (35.5%) displayed abnormal signal changes on gray matter, while 40 patients (52.6%) displayed abnormal white matter signal changes. Fifteen patients (19.7%) displayed signal changes on both white and gray matter, while 40

Table 1. Patient characteristics.

	Pharmaco-resistant (52)	Pharmco-responsive (24)	P-value
Age of onset	4.05 ± 0.57 (2.6, 0 - 16.5)	5.90 ± 0.98 (4.15, 0.1 - 15)	0.094
Female, n (%)	27 (51.9)	12 (50.0)	0.876
Location (F/C/T/P/O)	(28/5/8/6/5)	(12/2/3/6/1)	0.614
Mental retardation, n (%)	19 (36.5)	7 (29.2)	0.808
Full-scale IQ	75.89 ± 37.59 (91, 20-129)	71.17 ± 8.15 (62, 53-97)	0.769
Duration of epilepsy, years	6.20 ± 0.96 (5.4, 0.2 - 16.4)	7.59 ± 1.65 (5, 0.1-23)	0.842
Duration of treatment, years	6.08 ± 0.88 (5.65, 0.7 - 19)	8.20 ± 1.60 (5.2, 0-23)	0.202
Surgery, n (%)	22 (42.3)	2 (8.3)	
Pathologic Type I, n (%)	8 (15.4)		
Type IIa	6 (11.5)		
Type IIb	8 (15.4)	2 (8.3)	
N. of attempted antiepileptic drugs (%) 1	7 (13.5)	8 (33.3)	
2	8 (15.4)	7 (29.2)	
3	12 (23.1)	3 (12.5)	
4	5 (9.6)	2 (8.3)	
≥ 5	20 (38.5)	4 (16.7)	

F, frontal; C, central; T, temporal; P, parietal; O, occipital; IQ, intelligence quotient; N, number.

patients (52.6%) displayed abnormal white matter signal changes. Fifteen patients (19.7%) displayed signal changes on both white and gray matter, and significantly more patients in the pharmacoresistant group displayed both signal changes (25.0% vs. 8.3%, p = 0.124). There were no between-group differences with regards to the percentage of transmantle sign, hyperintense signal changes of the cortex on T2W images or on FLAIR images, or hyperintense signal changes of white matter on T2W images or on FLAIR images. Additional features are listed in Table 2.

Radiologic subtypes of focal cortical dysplasia according to MRI features and signal changes

Of 76 patients, 23 (30.3%) had a dominant white matter change, while 24 (31.6%) had a dominant cortical change. Twenty-nine patients (38.2%) had diffuse signal changes involving both white matter and the cortex. In 21 patients (27.6%), cortical signal intensity on T2W images was increased, while in 8 patients (10.5%), cortical signal intensity was decreased or isointense. Diffuse low/iso cortical SI on T2-WI type had an earlier age-of-onset compared to other subtypes (p = 0.01) and a lower full-scale IQ (P = 0.003). Diffuse type with low cortical SI consisted of 3 FCD type IIa patients and 2 FCD type IIb patients, while diffuse hypointense SI type consisted of 2 FCD type IIa patients and no

Table 2. Magnetic resonance imaging findings in pharmacoresistant or pharmacoresponsive group

	Pharmaco-resistant (52)	Pharmaco-responsive (24)	P-value
Thick cortex, n (%)	31 (59.6)	15 (62.5)	0.811
Volume change, n (%)	6 (11.5)	8 (33.3)	0.315
Abnormal gray matter, n (%)	19 (36.5)	8 (33.3)	0.786
High SI on T2WI	8 (15.4)	3 (12.5)	0.74
Low SI on T2WI	4 (7.69)	3 (12.5)	0.5
High SI on T1WI	4 (7.69)	1 (4.17)	0.564
High SI on FLAIR	14 (26.9)	4 (16.7)	0.328
Abnormal WM, n (%)	27 (51.9)	13 (54.2)	0.856
High SI on T2WI	20 (38.5)	11 (45.8)	0.543
Low SI on T2WI	3 (5.8)	1 (4.2)	0.771
High or Low SI on T1WI	15 (28.8)	6 (25.0)	0.927
High SI on FLAIR	23 (44.2)	12 (50.0)	0.639
Single SI changes, n (%) (GM or WM)	20 (38.5)	17 (70.8)	0.013
Double SI change, n (%) (GM and WM)	13 (25.0)	2 (8.3)	0.124
Transmantle sign, n (%)	12 (23.1)	3 (12.5)	0.282

SI, signal intensity; T2WI, t2-weighted image; T1WI, t1-weighted image; FLAIR, fluid attenuated inversion recovery; GM, gray matter; WM, white matter.

FCD type IIb patients. However, most of the FCD type IIb patients were included in the white matter type (Table 3). Seizure outcome did not differ between different subtypes (Table 4). Radiologically, more patients with the diffuse low cortical SI type displayed cortical thickening and volume changes, while the white matter type or gray matter type showed less volume changes (Table 5).

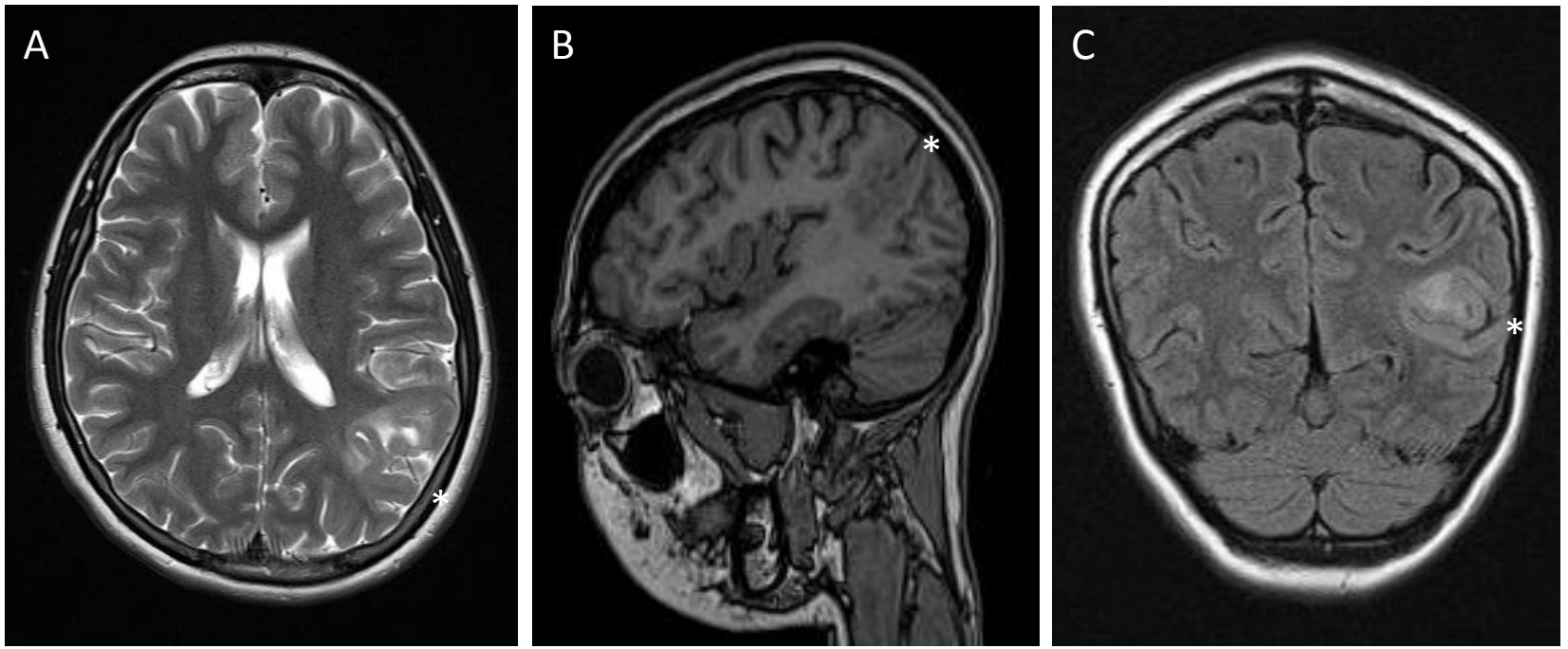

Figure 3. White matter type focal cortical dysplasia in a 3-year-old-girl. (A) Axial T2-weighted MRI shows severe hyperintense signal changes in the left parieto-occipital region. The margin between the cortex and white matter is blurred on the T1-weighted sagittal image (B), but is discernible on the coronal fluid-attenuated inversion recovery (FLAIR) image (C).

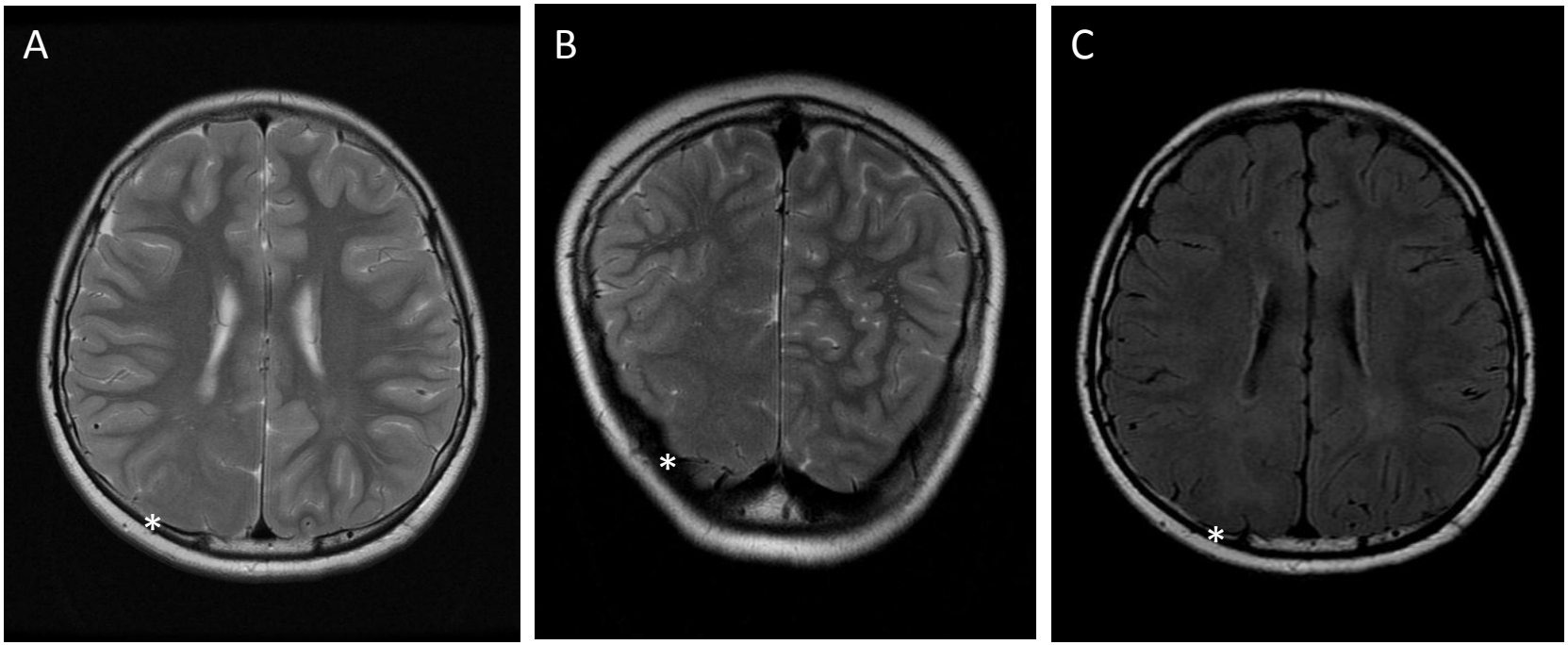

Figure 4. Diffuse type focal cortical dysplasia in an 8-year-old boy. (A) Axial and (B) coronal T2-weighted images show hypointense signal changes in the right occipital cortex. (C) Axial FLAIR image also shows low signal changes in the lesion.

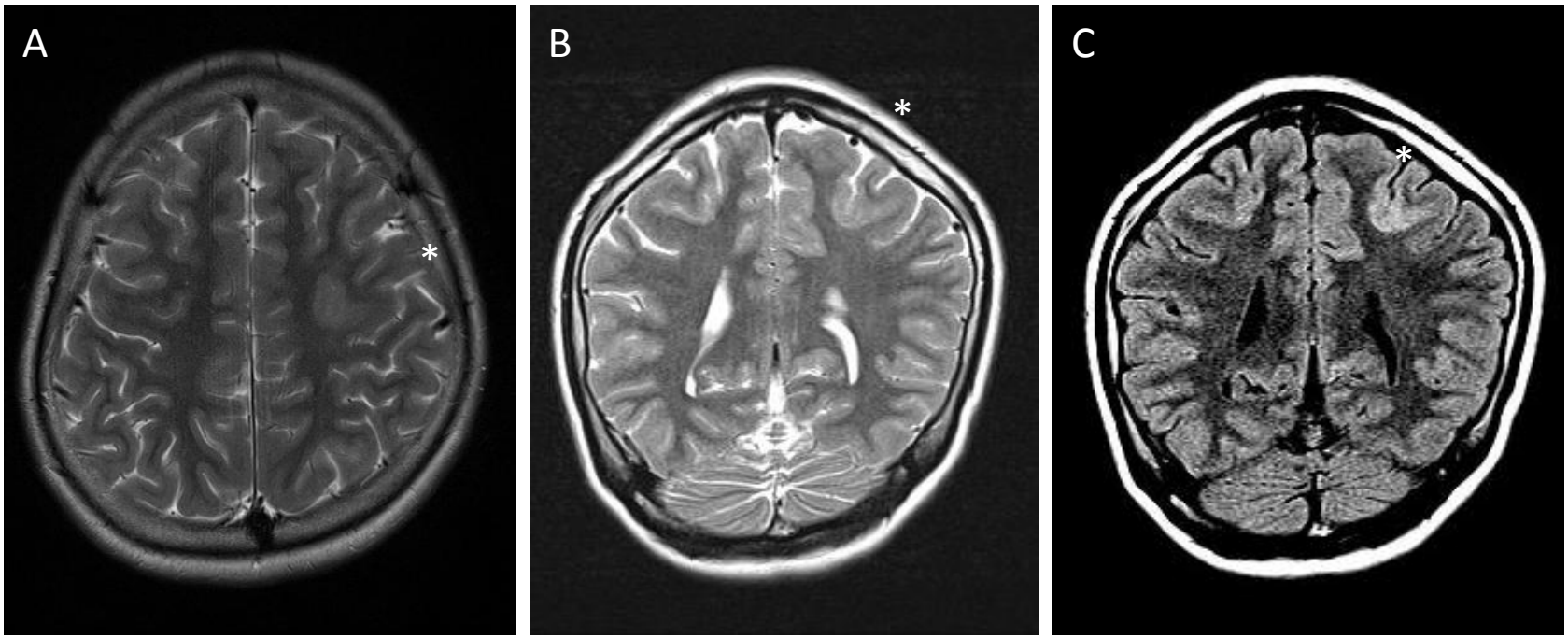

Figure 5. Gray matter type focal cortical dysplasia in an 18-year-old woman. (A) T2-weighted axial and (B) coronal images show an abnormal, thickened cortex with mild hyperintense signal changes in the left frontal lobe. (C) Coronal FLAIR image shows more prominent signal changes in the lesion.

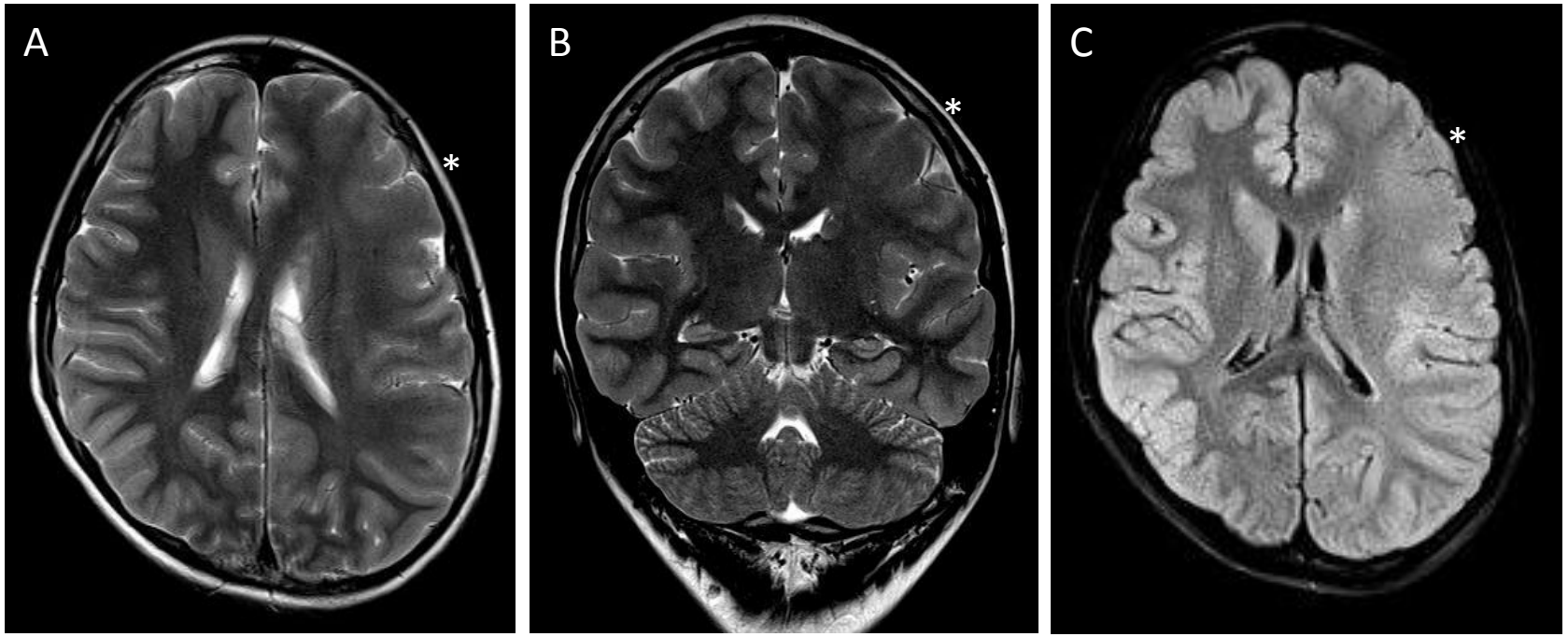

Figure 6. Extended gray matter type focal cortical dysplasia in a 13-year-old girl. (A) Axial and (B) coronal T2-weighted images show a blurring of the gray-white matter junction with severely involved cortex in the left frontal lobe. (C) Axial FLAIR image shows mild hyperintense signal changes in the lesion.

Table 3. Clinical features of radiologic subtypes.

	White matter type (23)	Diffuse type (8)	Gray matter type (24)	Extended gray matter type (21)	P-value
Age of onset	5.56 ± 0.93 (3.7, 0.3 - 14.5)	0.85 ± 0.40 (0.35, 0 - 3.2)	4.46 ± 0.83 (3.65, 0.1 - 15)	5.24 ± 1.06 (2.8, 0 - 16.5)	0.01
Female, n (%)	10 (43.5)	6 (75.0)	12 (50.0)	11 (52.4)	0.496
Location (F/C/T/P/O)	(10/1/4/6/2)	(6/0/0/1/1)	(14/5/0/4/1)	(10/1/7/1/2)	0.057
Mental retardation, n (%)	2/16 (12.5)	6/8 (75.0)	6/18 (33.3)	12/21 (57.1)	0.008
FSIQ, n (%)	98.71 ± 5.57 (96, 76 – 125)	37.5 ± 13.00 (37.5, 15 – 60)	92.75 ± 8.91 (93, 55 – 19)	64.90 ± 9.14 (61.5, 15 – 127)	0.003
Surgery, n (%)	9 (39.1)	4 (50.0)	3 (12.5)	7 (33.3)	0.009
Pathology, (I/IIa/IIb)	(2/0/7)	(0/3/1)	(1/1/1)	(5/2/0)	0.006

F, frontal; C, central; T, temporal; P, parietal; O, occipital; FSIQ, full scale intelligence quotient; N, number.

Table 4. Seizure outcome according to radiologic subtypes.

	White matter type (23)	Diffuse type (8)	Gray matter type (24)	Extended gray matter type (21)	P-value
Pharmacoresponsiveness, n (%)	8 (34.8)	3 (37.5)	6 (25.0)	7 (33.3)	0.861
Epilepsy duration	5.03 ± 1.07 (3.9, 0.1 - 17,1)	9.30 ± 2.12 (10.5, 1 - 16.3)	6.48 ± 0.99 (6.2, 0.2 – 16)	7.34 ± 1.49 (7.0, 0.5 - 23.0)	0.228
Daily seizure, n (%)	12 (52.2)	4 (50.0)	15 (62.5)	9 (42.9)	0.622
Generalized-tonic-clonic seizure, n (%)	9 (39.1)	6 (75.0)	12 (50)	10 (47.6)	0.379
Status epilepticus, n (%)	1 (4.3)	2 (25.0)	3 (12.5)	3 (14.3)	0.441
Epilepsia partialis continua, n (%)	3 (13.0)	3 (37.5)	5 (20.8)	3 (14.3)	0.438

Table 5. Magnetic resonance imaging features of different radiologic subtypes

	White matter type (23)	Diffuse type (8)	Gray matter type (24)	Extended gray matter type (21)	P-value
Thick cortex, n (%)	8 (12.5)	7 (87.5)	19 (79.2)	12 (57.1)	0.006
Volume change, n (%)	2 (8.7)	6 (75.0)	0 (0.0)	6 (28.5)	<0.0001
Abnormal GM SI, n (%)	5 (21.7)	6 (75.0)	11 (45.8)	5 (23.8)	
High SI on T2WI	2 (8.7)	1 (12.5)	5 (20.8)	3 (14.3)	
High SI on T1WI	1 (4.3)	2 (25.0)	1 (4.2)	1 (4.8)	
High SI on FLAIR	4 (17.4)	0 (0.0)	9 (37.5)	4 (19.0)	
Abnormal WM SI n, (%)	23 (100.0)	5 (62.5)	7 (29.2)	5 (23.8)	
High SI on T2WI	23 (100.0)	0 (0.0)	4 (16.7)	4 (19.0)	
High or Low SI on T1WI	16 (69.6)	2 (25.0)	2 (8.3)	1 (4.8)	
High SI on FLAIR	23 (100.0)	1 (12.5)	6 (25.0)	5 (23.8)	

SI, signal intensity; T2WI, t2-weighted image; T1WI, t1-weighted image; FLAIR, fluid attenuated inversion recovery; GM, gray matter; WM, white matter.

Discussion

In this study, 31.6% (24/76) of the patients showed a good response to antiepileptic drugs (≥2-year seizure freedom), and this group was more likely to have a lesion confined to the cortex or to the white matter than the pharmacoresistant group did.

Although pharmacoresponsiveness in patients with FCD has not been frequently discussed, patients with a more benign outcome have been reported occasionally in the literature. For example, apparently asymptomatic FCD lesions have been identified on MRI screenings of other disorders [14,15]. Additionally, there are reports of successful treatment of patients with FCD by using pharmacologic intervention, as two earlier studies on FCD reported 16.7% of patients (2/12, 20/120) [13,16] to be drug-responsive (>1-year seizure freedom while receiving medical treatment). Remarkably, one recent study showed that 25.8% (16/62) of patients with FCD had prolonged seizure-free periods, including 2 patients whose seizures were controlled for up to 20 years [8].

The study presented here reported a higher than expected percentage of pharmacoresponsive patients with FCD, probably because this study included the patients with FCD who were identified radiologically. This study is believed to be the first to assess subjects who responded to medical therapy and did not receive surgery. Previous studies have

focused on the population of patients whose seizures were not controlled by pharmacologic treatments and underwent surgery. The observed success of AED treatment in this study may be attributed, in part, to the recent advances in neuroimaging techniques that probably enhanced the detection of small, subtle lesions, which may have more benign outcomes than the larger lesions detected with conventional MRI in previous studies. Additionally, the development of new AEDs may In the current study, there were 3 patients who succeeded in weaning off of AEDs, although the permanence of this status will have to be determined through future follow-up. One patient was a 7-year-old boy with a left frontal FCD lesion. His seizures began when he was 3 months old, as fever-provoked, right-sided, clonic seizures. Then, epileptic spasms and atonic head drops occurred for the following 7 months; however, he responded to oral steroid therapy. Before steroid, phenobarbital, phenytoin, vigabatrin, zonisamide, and lamotrigine had been ineffective. At 4 years old, the patient was weaned off of all AEDs, and he has been seizure-free since (approximately 3 years without seizure). The second patient was a 5-year-old boy with a right temporo-occipital FCD lesion. When he was 2 years old, right temporo-occipital onset focal seizures occurred in clusters, often progressing to generalized tonic-clonic seizures. Valproic acid, topiramate, levetiracetam, and carbamazepine were tried, and although seizures

persisted for a month, they eventually subsided. He has been seizure free for 3 years and has not been on AEDs for 9 months. The third patient was a 7-year-old girl with a left parietal FCD lesion. She had asymmetric tonic seizures affecting the right side of her head, which began when she was 3 years old. Seizures persisted for 3 months, and subsided with the addition of levetiracetam to oxcarbazepine. She has been seizure-free without any AEDs for a year and 6 months now. In these 3 patients, localized EEG abnormalities improved with AEDs, and their EEGs remained normal after cessation of AED treatment.

Pharmacoresponsiveness in FCD has not been widely studied, possibly because of the lack of pathologic diagnosis, lack of extensive evaluation in this group, and lack of interest. The current study showed that a higher number of FCD patients respond to the medical therapy than previously expected. Few patients succeeded in weaning off of the AEDs. However, the drug-responsive group did have a longer duration of epilepsy and a longer duration of medical treatment, suggesting that most patients with FCD have chronic epilepsy. In order to optimize treatment for individual patients with FCD, identifying different subgroups of FCD with different outcomes is necessary.

In this study, a single signal change, limited to the cortex or to the white matter, was more commonly found in the pharmacoresponsive group, while signal changes involving both cortex and white matter

tended to occur more frequently in the pharmacoresistant group. A large FCD-related lesion involving the multilobar area has been consistently reported as a predictive factor for poor surgical outcome [17,18]; however, there have been no studies that have evaluated treatment outcome according to the vertical extent of the lesion. It would be interesting to confirm these findings in a larger study.

The mechanism underlying the signal intensity changes in the FCD lesions remains unknown, though different distribution of abnormal cell components is one plausible hypothesis. Dysmorphic neurons can be distributed throughout the entire cortex or located within the white matter [1]. The presence of activated microglia within the FCD lesion has been confirmed by an imaging study [19] and an immunohistochemical study [20]. Further studies that aim to delineate a clear relationship between MRI findings and separate histological findings in the cortex and white matter might be beneficial.

In the current study, specific MRI features that predicted the treatment outcome could not be identified, even after a thorough review of the scans. Previous surgical series have shown similar results, failing to find any MRI features that could specifically differentiate between FCD subtypes or predict the surgical outcome except a transmantle sign [21]. FCD is considered to represent a heterogeneous group of cortical lesion disorders with various etiologies.

Although FCD type II is considered to be a more homogeneous group compared to FCD type I, it is still difficult to define this group due to the diverse clinical, radiological, and histological features. A broad spectrum of radiological findings, including normal images, tuber-like lesions, and lesions that are more diffuse have been observed within the FCD type IIB [8]. Pathologically, different findings in “Mild” and “Severe” FCD type IIb have been suggested to be associated with different level of myelin deficiency, and different oligodendroglia and balloon cell numbers using immunohistochemical and histopathologic evaluation [22]. Different subpopulations within the FCD type IIa regarding different myelin content and oligodendroglial cell numbers have also been reported. Recently, evidence of various types of dysmorphic neurons with different origins has been reported in FCD patients [23,24]. Further studies are required to define correlations among different pathologic findings, different MRI features, and different clinical outcomes.

When the images were classified based on the degree of disturbance in the gray-white matter junction and the signal intensity of T2W images, one group showed different features than the other group: this group had a severely disturbed gray-white matter junction border and concurrent hypointense/isointense or mild hyperintense signal changes on T2W images, resembling the images of hemigalencephaly. Patients

in this group presented with an earlier onset of epilepsy and more severe neurocognitive dysfunction. Four patients who underwent the resection were diagnosed with either FCD type IIa or IIb. MRI of younger children with unmyelinated brains may have caused the signal changes, and 2 of the children within this group were younger than 1 year of age (1 year old and 8 months old); however, this does not explain the observed changes on MRI in older children.

A variant of FCD type II that resembles hemimegalencephaly, and which has a poor prognosis, has been proposed by earlier studies. One previous study divided cortical dysplasia of Taylor (CDT) into 2 groups based on histopathology and immunohistochemical findings, and reported that the CDT-dysplastic type in comparison to the CDT-balloon cell type showed pathologic characteristics identical to those of hemimegalencephaly and had a more severe phenotype, a lower IQ, an earlier age of epilepsy onset, a higher rate of multilobar surgery, and a lower rate of seizure freedom at 2 years following surgery [25]. A variant form of FCD has also been reported under the term of “posterior quadrant dysplasia” or “hemi-hemimegalencephaly.” This type is associated with an early seizure onset, refractory epilepsy, mental retardation, and mild hemiparesis [26,27]. In a previous study that reviewed 18 children with either hemimegalencephy or FCD, hypointense signal changes on T2W were reported in all patients with

hemimegalencephaly (2/2) and in some patients with FCD (5/9) [28]. According to the "Developmental and genetic classification for malformations of cortical development: update 2012" suggested by Barkovich, FCD type II is classified together with hemimegalencephaly as "cortical dysgenesis with abnormal cell proliferation but without neoplasia"[29]. Further evaluation with a larger sample size is needed in order to elucidate whether there is an isolated variant within the FCD type IIb group that displays uniform radiologic and histological features and distinguishable clinical outcomes.

This study had its limitations. Although many specific MRI features for FCD were assessed to increase the accuracy of its detection, there remains the possibility of false positives and false negatives with regards to the FCD diagnosis as they were not pathologically confirmed. Patients with a histologic diagnosis of cortical dysplasia and had normal MRI scans were excluded, and this may have hindered us from understanding or evaluating the whole population. However, this study does offer a potential prediction factor for FCD patient pharmacoresponsiveness and clinical outcome without invasive surgery, while contributing to the literature on the early identification of patients with refractory epilepsy or poor clinical outcome.

Conclusion

Some FCD patients responded better to the AEDs than others. The extent of signal changes in the lesion area might predict the responsiveness to medical therapy. A small group of FCD patients showed distinguishable MRI features that coincided with poor clinical outcome. Further studies are required to confirm these findings.

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피질이형성증의 약물반응도와 관련된 자기공명영상 소견

배경: 피질이형성증은 소아 난치성 뇌전증의 흔한 원인이다. 다양한 임상양상이 알려져 있지만, 예후 예측인자는 잘 알려져 있지 않다. 본 연구에서 저자들은 자기공명영상 소견을 사용하여 피질이형성증의 약물순응도에 대한 예후 예측인자를 발견하고자 하였다.

방법: 난치성 뇌전증 및 피질이형성증 영상소견을 보이는 소아 청소년 환자 총 76 명의 뇌 자기공명영상을 확인하였다. 항경련제를 사용하여 2년간 경련이 없는 환자를 약물반응군으로 분류하고, 뇌자기공명영상 소견과 약물반응도와의 관련성을 평가하였다. 추가로 뇌자기공명영상 소견에 따라 환자를 4군으로 나누고 임상양상을 비교하였다.

결과: 약물반응군과 약물비반응군과의 사이에 유의한 차이를 보이는 특정 뇌자기공명영상 소견은 발견되지 않았다. 그러나, 두 군을 비교하였을 때 약물반응군에서는 비반응군에 비하여, 많은 환자가 뇌의 피질이나 백질, 한 군데에 국한된 신호양상의 차이를 보인 반면 (70.8% vs. 38.5%, p = 0.013), 약물비반응군에서는 반응군에 비하여 더 많은 환자가 뇌의 피질과 백질, 두 곳을 모두 포함한 넓은 부분에서 신호양상의 차이를 보였다 (25% vs. 8.3%, p = 0.028). 뇌자기공명영상 소견에 따라 환자를 분류하였을 때는 T2 영상에서 저하된 신호양상을

보이며, 이상한 피질의 모양과 백질 이상을 동반한 넓은 병변을 보인 환자군이 다른 환자군에 비해 경련 시작 나이가 더 어렸으며, 더 심한 인지기능 저하를 보였다.

결론: 본 연구는 피질이형성증 환자들이 항경련약물 치료에 다양하게 반응하며, 자기공명영상에서 신호양상으로 구분되는 주요 병변의 범위로 약물반응을 예측할 수 있음을 시사한다.

주요어 : 피질이형성증, 소아, 뇌자기공명영상, 뇌전증, 예후, 항경련제

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