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Compatibility of MRI and FDG-PET findings with histopathological results in patients with focal cortical dysplasia

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ABSTRACT

Purpose: The present study aimed to determine if the specific characteristics of fluorodeoxyglucose-positron emission tomography (FDG-PET) analyses of the FCD subgroups were compatible with the magnetic resonance imaging (MRI) and clinical findings of the patients in these subgroups.
Methods: This study included 71 patients who had a presurgical evaluation workup performed due to drug-resistant seizures, who underwent epilepsy surgery, and who were histopathologically diagnosed with FCD. Relationships involving MRI and FDG-PET findings and clinical data from pathological subgroups and patients were assessed.
Results: According to the International League Against Epilepsy (ILAE) classifications of FCD, 28 of the patients were type I and 43 were type II. FCD was visible on the MRI scans of 53 patients, and a majority of this group was classified as type II FCD (n = 34). Of these 53 patients, FCD was located in the temporal area of 21 patients, the extratemporal area of 29 patients. Of the patients who exhibited FDG-PET hypometabolism (PET-positive), 23 were classified as temporal, 17 as frontal, 11 showed involvement of the posterior cortex. The age of seizure onset was younger in PET-positive patients ($p = 0.032$), and histopathological analyses revealed that 23 patients had type I FCD and 30 patients had type II FCD.
Conclusion: PET scans reveal a lesion by showing hypometabolism in patients who have refractory epilepsy and an early age of onset with FCD. The lesions of MRI-negative/PET-positive FCD patients tend to be localized in the temporal lobe and that FCD may be localized in the frontal lobe of MRI-negative/PET-negative patients. However, the histopathological examinations of MRI-positive/PET-positive, MRI-negative/PET-positive, and MRI-negative/PET-negative patients did not exhibit a particular histopathological subtype.

1. Introduction

Focal cortical dysplasia (FCD) is a cortical developmental disorder that manifests during brain maturation and frequently causes refractory seizures that commence at early ages. Recent developments in diagnostic methods have made significant contributions to the delineation of the epileptogenic zones associated with FCD and have enabled better definition of surgical candidates and an increase in successful surgical outcomes. Nonetheless, some patients who have normal magnetic resonance imaging (MRI) findings that require further intracranial investigation prior to surgery are subsequently confirmed as having FCD after a histopathological evaluation. In such cases, positron emission tomography (PET), which is a functional neuroimaging method, may provide complementary information.

Studies investigating temporal lobe epilepsies (TLE) associated with hippocampal sclerosis have reported severe cell loss following pathological analyses, but the PET findings were not correlated with the severity of the MRI findings or PET hypometabolism [1]. Fluorodeoxyglucose (FDG)-PET-positive and MRI-negative TLE patients typically have successful surgical outcomes [2], but there is a lack of adequate information regarding the PET findings of patients with FCD. Thus, the present study aimed to determine the compatibility of the characteristics of the

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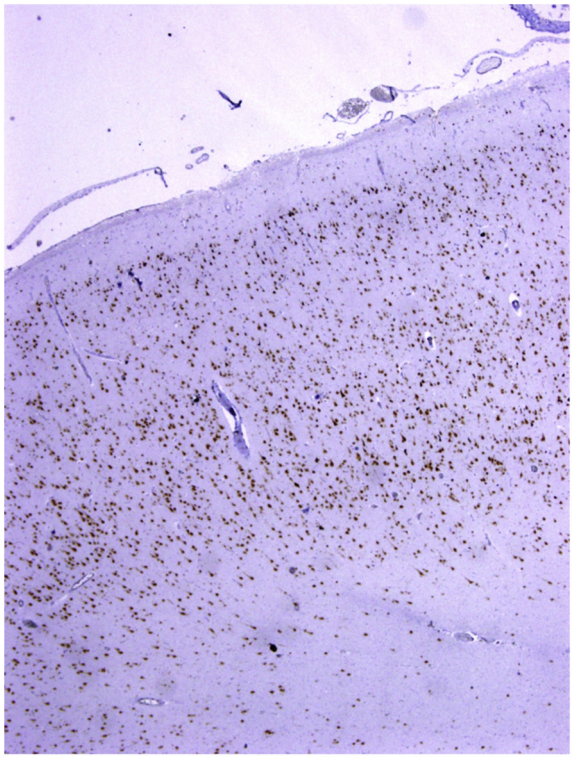

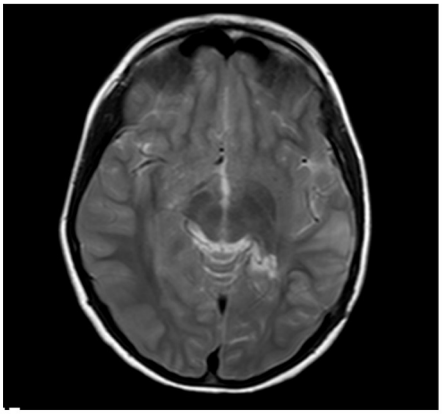

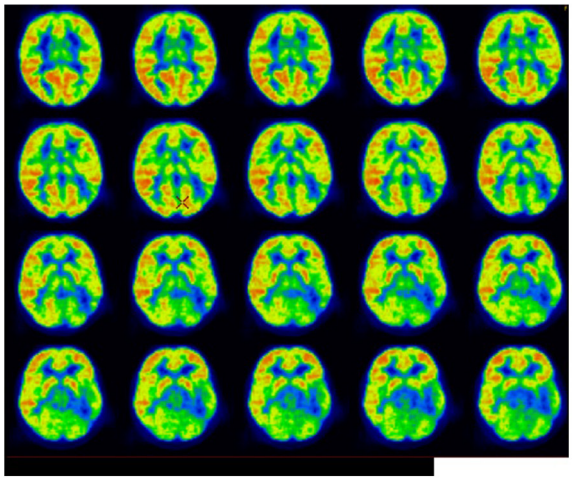

Fig. 1. A case report: A patient with refractory epilepsy to drug therapy. She was born in 2003, who was admitted when she was 7-years-old. Her first seizure occured at 6 months of age. Interictal and ıctal EEG recording indicate left temporal region. MRI showed cortical and subcortical signal abnormalities on axial T2WI in the left temporal lobe. FDG-PET/CT images demonsrated hypometabolism in the temporal lobe extending also occipital area at left. Resective surgery was planned to the patient, intracranial electrode were not used. Postoperative histopatological examination confirmed 'type Ib, focal cortical dysplasia' (Figure: Six layered cortex with patchy neuronal cell loss-FCD ILAE Type Ib (Neu-NX100)). The patient is currently seizure-free (Engel I).

MRI and PET findings of various FCD histopathological subgroups. Furthermore, this study investigated whether there are common features among PET-positive and MRI-negative patients in terms of histopathological subtype, demographic variables, electrophysiological findings, and lesion localization.

2. Materials and methods

2.1. Study design and population

The present study was a retrospective analysis of 71 patients who underwent surgery for refractory epilepsy between 1997 and 2015 at Istanbul University, Cerrahpaşa Faculty of Medicine. All patients had a histopathological diagnosis of FCD, underwent a standard presurgical evaluation workup that included both interictal and ictal video-electroencephalography (VEEG) monitoring, cranial MRI and FDG-PET scans, and neuropsychological and neuropsychiatric examinations. Patients for whom it was possible to determine an epileptogenic zone during phase I investigations underwent surgical interventions, and all other patients completed additional intracranial recordings (Fig. 1: a case report). The data from the patients who had been diagnosed with FCD were reviewed and analyzed.

2.2. Inclusion and exclusion criteria

Patients of any age who received surgical treatment for refractory epilepsy and were diagnosed with either type I or type II FCD according to the International League Against Epilepsy (ILAE) classifications were included in the present study. Patients whose EEG, MRI, and/or PET examination data could not be obtained and/or patients who did not undergo such tests to determine the epileptogenic zone were not included in the present study. Additionally, patients with a type III ILAE FCD classification (the presence of hippocampal sclerosis, a glial or glioneuronal tumor, FCD in an adjacent vascular malformation, trauma accompanying the early childhood period, an ischemic event, or other accompanying lesion, such as encephalitis) were excluded from the study.

2.3. Evaluation of patient data

In the present study, information such as age at seizure onset, duration of epilepsy, age at surgery, and post-operative follow-up periods were collected and analyzed. Evaluations of post-operative seizure control were carried out based on the Engel classification. To this end, patients were assessed during a follow-up examination or contacted via phone, and both the patient and their close relatives were interviewed.

2.4. Evaluation of pathological tissues

Tissue samples obtained during surgery were collected using serial sections, and routine hematoxylin and luxol fast blue stains were then applied. Additionally, immunohistochemical analyses assessing glial fibrillary acidic protein (GFAP), neuron-specific nuclear protein (NeuN), SMI-311, and Vimentin were performed. The histopathological subcategorization of FCD was initially conducted using the Palmini classification, and the tissue preparations were then reanalyzed by two independent and

experienced pathology specialists blind to the clinical information of the patients. Finally, the samples were re-classified based on the novel FCD definitions recently described by the ILAE [3].

FCD type I was defined as cortical lamination disorder without dysmorphic or balloon cells; this diagnosis was considered to be Ia in the presence of a disorder of the radial alignment in the cortical lamination, Ib in the presence of a tangential change, and Ic in the presence of both radial and tangential disorders. Diagnoses were considered to be type IIa if dysmorphic neurons were present without balloon cells, and they were considered type IIb if balloon cells accompanied dysmorphic neurons. Thus, the FCD was classified as follows: types Ia, Ib, and Ic and types IIa and IIb. Additionally, all patients underwent interictal and ictal VEEG monitoring as part of the presurgical evaluation; 39 needed additional intracranial recordings due to inconsistent or inconclusive non-invasive data or negative imaging results (Fig. 1: a case report).

2.5. Evaluation of the imaging tests

The cranial MRI scans were performed with a 1.5 Tesla MRI scanner in conjunction with an epilepsy protocol. For cases in which the 1.5 Tesla MRI results were uncertain, a 3 Tesla MRI examination was performed. All MRI scans of the patients in the present study included T_1-weighted, T_2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences.

All FDG-PET scans were conducted during the interictal period at least 24 h after the last seizure as described in methods to eliminate the influence on PET sensitivity. The cranial MRI and FDG-PET examinations were visually re-evaluated by a neurosurgeon (MU) and nuclear medical specialists (BV, MH), respectively, to determine the characteristics of the lesion. These tests were initially performed independently and then subsequently re-evaluated by the group. The individuals who assessed patient information were unaware of the clinical histories of and EEG findings for the patients.

An MRI was termed as MRI-positive when a lesion was observed and MRI-negative when a lesion was not observed. Similarly, PET scans were termed PET-positive when hypometabolism was observed and PET-negative when hypometabolism was not observed. Established lesions on MRI and/or PET scans were grouped as follows according to their localization: frontal, temporal, parietal, occipital, or multilobar (lesions with vast localizations in more than one lobe) (Fig. 1: a case report)

2.6. Statistical analysis

All analyses were conducted using SPSS 15.0 software (Statistical Package for Social Sciences, SPSS Inc.; Chicago, IL, USA). Digital data are presented as means ± standard deviations (SD), frequencies, and percentages, and chi-square tests were used to compare categorical variables. P-values < 0.05 were considered to indicate statistical significance.

2.7. Ethical approval

Approval for the present study was issued by Istanbul University, Cerrahpaşa Faculty, Medical Ethics Committee (number 83045809/3508).

3. Results

3.1. Evaluation of demographic data

The present study included 71 patients (42 females and 29 males). According to the histopathological examinations, 28 of these patients (39.44%) were type I FCD and 43 (60.56%) were type II FCD. The demographic characteristics of and findings for the patients are summarized in Table 1. The lesions were localized in the temporal area of 27 patients, the frontal area of 28 patients, and the parieto-occipital area of 14 patients, and they were multilobar in two patients.

An examination of seizure duration according to age of seizure onset revealed that the mean duration was 10.4 years in patients who developed epilepsy before 18 years of age (n = 62) and 14 years in patients who developed epilepsy after 18 years of age (n = 9). In the former group, 40% of the patients had type I FCD and 69% had type II FCD; 75.81% of this group were PET-positive, 24.19% were PET-negative, 72.58% were MRI-positive, and 27.42% were MRI-negative (Table 2).

Based on age at surgery, the mean duration of seizures was 7.8 years in the 31 patients who underwent surgery before 18 years of age and 17.86 years in the 40 patients who underwent surgery after18 years of age. In the former group, 67.74% of the patients had type II FCD and 83.87% were PET-positive, 16.13% were PET-negative, 80.65% were MRI-positive, and 19.35% were MRI-negative. In the latter group, 55% of the patients had type II FCD and 67.5% were PET-positive and 70% were MRI-positive.

There were no statistically significant differences between the groups categorized by age of seizure onset and age at operation in terms of the pre-operative PET or MRI findings or the post-operative histopathological results (Table 2).

3.2. Comparison of MRI-positive and MRI-negative patients

In the present study, 53 patients (74.65%) exhibited FCD on the MRI scan (MRI-positive); these lesions were located in the temporal lobe of 21 patients (11 with type I and 10 with type II), the frontal lobe of 19 patients (five with type I and 14 with type II), and the parietal lobe of 10 patients (two with type I and eight with type II); they were multilobar in three patients (two were type IIa, and one was type I). Temporal lobe involvement was more common in almost all of the similar histopathological groups, but FCD type II was more frequent in the frontal and parietal lobes, even though this difference was not statistically significant (p = 0.192).

All 18 patients in the MRI-negative group underwent invasive recordings; these revealed lesions in the frontal area of eight

Table 1
Demographic characteristics of patients. (ASO: age of seizure onset).

	All FCD patients	Female	Male	Type I	Type II
ASO	8.39 ± 7.63 (0.1–30)	5.50 ± 7.50 (0.1–30)	7.0 ± 7.93 (0.1–30)	9.0 ± 6.59 (0.6–24)	5.0 ± 8.27 (0.1–30)
Duration of epilepsy	13.57 ± 9.34 (0.1–41)	13.0 ± 10.39 (0.1–41)	10.0 ± 7.23 (0.4–28)	13.0 ± 7.37 (1–26)	12.0 ± 10.47 (0.1–41)
Age at surgery	21.93 ± 11.4 (0.4–51)	23.0 ± 12.39 (0.4–51)	20.0 ± 9.76 (7–44)	9.0 ± 6.59 (0.6–24)	5.0 ± 8.27 (0.1–30)
Total	71	42 (59.15%)	29 (40.85%)	28 (39.44%)	43 (60.56%)

Table 2
Demographic data of patients according to age at surgery and seizure onset.

	Age of seizure onset		Age at surgery	
	<18 years	>18 years	<18 years	>18 years
ASO	5.79 (0.1–17)	23.5 (18–30)	5.05 (0.1–13)	11.53 (1–30)
Duration of epilepsy	14.81 (0.1–38)	10.4 (3–24)	7.8 (0.1–16)	17.86 (3–41)
Age at surgery	20.32 (0.4–51)	33.8 (23–44)	10.89 (0.4–17)	29.37 (18–51)
Type I FCD	25 (40.32%)	3 (33.33%)	10 (32.26%)	18 (45%)
Type II FCD	37 (69.68%)	6 (66.66%)	21 (67.74%)	22 (55%)
PET-positive	47 (75.81%)	6 (66.66%)	26 (83.87%)	27 (67.5%)
PET-negative	15 (24.19%)	3 (33.33%)	5 (16.13%)	13 (32.5%)
MRI-positive	45 (72.58%)	8 (88.88%)	25 (80.65%)	28 (70%)
MRI-negative	17 (27.42%)	1 (11.11%)	6 (19.35%)	12 (30%)
Total	62	9	31	40

Table 3
Comparison of MRI-positive, MRI-negative, PET-positive, and PET-negative patients.

	MRI-positive (n%)	MRI-negative (n%)	p value	PET-positive (n%)	PET-negative (n%)	p-value
FCD Type I	19 (35.35)	9 (50)	0.289	23 (43.40)	6 (33.33)	0.241
FCD Type II	34 (64.15)	9 (50)		30 (56.60)	12 (66.66)	
Frontal	19 (35.85)	8 (44.44)	0.257	17 (32.07)	10 (55.55)	0.099
Temporal	21 (39.62)	6 (33.33)		23 (43.39)	5 (27.77)	
Parietal	10 (18.87)	3 (16.6)		10 (18.87)	3 (16.66)	
Occipital	–	1 (5.55)		1 (1.89)	–	
Multilobar	3 (5.66)	–		2 (3.78)	–	
Age at onset	7 ± 7.74	5.5 ± 7.49	0.843	5 (0.1-30)	9.5 (1-30)	**0.032***
Duration of epilepsy	12 ± 9.17	14.5 ± 9.58	0.140	12 ± 7.59	13 ± 13.12	0.543
Age at surgery	22 ± 11.66	24.5 ± 10.45	0.193	20 ± 10.07	26 ± 13.63	0.062
Total	53 (74.65)	18 (25.35)		53 (74.65)	18 (25.35)	

patients, the temporal area of six patients, the parietal area of three patients, and the occipital area of one patient. These locations were histopathologically confirmed after surgery, and nine were type I and nine were type II. The histopathological subgroups and lesion localizations of the MRI-positive and MRI-negative patients are provided in Tables 3 and 4.

3.3. Comparison of pre-operative PET-positive and PET-negative patients

Hypometabolism (PET-positive) was observed in 53 patients (74.6%); the locations were temporal in 23, frontal in 17, parietal in

Table 4
Histopathological subgroups and lesion localizations of MRI-positive, MRI-negative, PET-positive, and PET-negative patients.

	FCD	Temporal (n%)	Frontal (n%)	Parietal (n%)	Occipital (n%)	Multilobar (n%)	Total (n%)
MRI-positive	Ia	7 (33.33)	1 (5.26)	2 (20.0)	–	1 (33.33)	11 (20.75)
	Ib	4 (19.05)	4 (21.05)	–	–	–	8 (15.09)
	IIa	8 (38.09)	7 (36.84)	4 (40.0)	–	2 (66.66)	21 (39.62)
	IIb	2 (9.52)	7 (36.84)	4 (40.0)	–	–	13 (24.52)
Total		21 (39.62)	19 (35.85)	10 (18.87)	–	3 (5.66)	53 (74.65)
MRI-negative	Ia	2 (33.33)	–	–	1 (100)	–	3 (16.7)
	Ib	2 (33.33)	2 (25.0)	2 (66.66)	–	–	6 (33.3)
	IIa	4 (66.66)	3 (37.5)	–	–	–	7 (38.9)
	IIb	–	1 (12.5)	1 (33.33)	–	–	2 (11.1)
Total		6(33.33)	8 (44.4)	3 (16.66)	1 (5.55)	–	18 (25.35)
PET-positive	Ia	9 (39.13)	1 (5.88)	2 (20)	1 (100)	1 (50)	14 (26.41)
	Ib	5 (21.73)	3 (17.64)	1 (10)	–	–	9 (16.98)
	IIa	7 (30.43)	9 (52.94)	2 (20)	–	1 (50)	19 (35.84)
	IIb	2 (8.69)	4 (23.52)	5 (50)	–	–	11 (20.75)
Total		23 (43.39)	17 (32.07)	10 (18.86)	1 (1.88)	2 (3.77)	53 (74.65)
PET-negative	Ia	–	–	–	–	–	–
	Ib	2 (40)	2 (40)	1 (20)	–	–	5 (27.77)
	IIa	3 (33.33)	4 (44.44)	2 (22.22)	–	–	9 (50)
	IIb	–	4 (100)	–	–	–	4 (22.22)
Total		5 (27.77)	10 (55.55)	3 (16.66)	–	–	18 (25.35)

10, occipital in one, and multilobar in two patients. According to the histopathological classification of these 53 PET positive patients, 23 patients were type I and 30 were type II. There were 18 PET-negative patients where 6 of them type I and 12 were type II.

In other words in 29 patients with FCD type I, 23 patients had positive PET (79%) where in 42 patients with FCD type II, 30 of them (71%) had positive PET studies which demonstrates that in both groups majority of the patients showed PET hypometabolism. Further statstical analyses did not reveal any significance except for the age at seizure onset which was younger in PET-positive patients ($p = 0.032$). A comparison of the PET-positive and PET-negative patients is provided in Table 3.

3.4. Subgroup analyses of MRI and PET results

In the present study, 39 patients were MRI-positive/PET-positive; these lesions were temporal in 17 patients, frontal in 14 patients, and parietal in eight patients. According to the histopathological classification, 16 patients were type I and 23 were type II. Ten patients were MRI-positive/PET-negative; these lesions were temporal in four patients, frontal in three patients, and parietal in three patients. All patients, except for one with a lesion in the temporal lobe, were FCD type II (Table 5). Ten patients were MRI-negative/PET-positive; these lesions were temporal in five patients, frontal in two patients, parietal in two patients, and occipital in one patient, and 50% were type I FCD and 50% were type II FCD (Table 5). Eight patients were MRI-negative/PET-negative; these lesions were temporal in one patient, frontal in six patients, and parietal in one patient, and 50% were type I FCD and 50% were type II FCD (Table 5).

No statistically significant differences were found in the different subgroup analyses. Tables 6 and 7 show the histopathological subgroup classifications based on the lesion locations using the MRI and PET scans and the post-operative outcomes of seizures. Seizure outcomes were favorable in all groups.

All groups had very good outcome. There were total of 39 patients with MRI+/PET+ findings of which 37 had good and 2 had poor outcome. A total of 10 patients had MRG + /PET− findings. Among them 8 had good and 2 had poor outcome. There were total of 10 patients with MRG −/PET+ findings of which all of them had good outcome. A total of 8 patients MRI −/PET− findings. Among them 7 had good and 1 had poor outcome (Table 7).

4. Discussion

Although several studies have investigated relationships among the histopathological subgroups of FCD, relationships among the surgical outcomes of FCD patients who underwent MRI and PET scans have yet to be evaluated. Thus, the present study assessed the compatibility of the pre-operative MRI and PET findings of 71 FCD patients with their histopathological type of FCD.

4.1. Evaluation of clinical characteristics

Although FCD constitutes the most common cause of seizures in patients who undergo surgery prior to 18 years of age, it follows hippocampal sclerosis and tumors among those who undergo

Table 5
MRI-positive/PET-positive, MRI-positive/PET-negative, MRI-negative/PET-positive, and MRI-negative/PET-negative patients.

		Type Ia (n%)	Type Ib (n%)	Type IIa (n%)	Type IIb (n%)	Total (n%)
MRI-positive/PET-positive	FCD	11 (28.21)	5 (12.82)	13 (33.33)	10 (25.64)	39 (54.92)
	Frontal	1 (7.14)	3 (21.42)	6 (42.85)	4 (28.17)	14 (35.89)
	Temporal	7 (41.17)	3 (17.64)	5 (29.41)	2 (11.76)	17 (43.58)
	Parietal	2 (25)	–	2 (25)	4 (50)	8 (20.51)
	Total	16 (41.03)		23 (53.97)		39 (54.92)
	Age at onset	9.6 ± 7.23		5.64 ± 7.23		7.2 ± 7.5
	Duration of epilepsy	9.4 ± 6.75		12.98 ± 7.76		11.5 ± 7.4
	Age at surgery	18.93 ± 8.54		18.53 ± 11.49		18.7 ± 10.2
MRI-positive/PET-negative	FCD	–	1 (10)	6 (60)	3 (30)	10 (14.08)
	Frontal	–	–	1 (33.33)	2 (66.66)	3 (30)
	Temporal	–	1 (25)	3 (75)		4 (40)
	Parietal	–	–	2 (66.66	1 (33.33)	3 (30)
	Total	–	1 (10)	9 (90)		10 (14.08)
	Age at onset	–	9	13.0 ± 8.31 (4–30)		11 ± 7.9
	Duration of epilepsy	–	26	12.0 ± 15.21 (0.1–38)		16 ± 14.7
	Age at surgery	–	35	33.0 ± 15.04 (4–46)		33.5 ± 14.2
MRI-negative/PET-positive	FCD	3 (30)	2 (20)	4 (40)	1 (10)	10 (14.08)
	Frontal	–	–	2 (100)	–	2 (20)
	Temporal	2 (40)	1 (20)	2 (40)	–	5 (50)
	Parietal	–	1 (50)	–	1 (50)	2 (20)
	Occipital	1 (100)	–	–	–	1 (10)
	Total	5 (50)		5 (50)		10 (14.08)
	Age at onset	6.0 ± 6.65 (3–18)		4.0 ± 12.07 (1–30)		5 ± 9.1
	Duration of epilepsy	15.0 ± 4.15 (14–24)		10.0 ± 11.26 (4–28)		15 ± 8.07
	Age at surgery	27 ± 6.81 (18–33)		28 ± 11.23 (11–35)		27.5 ± 8.8
MRI-negative/PET-negative	FCD	–	4 (50)	3 (37.5)	1 (12.5)	8 (11.26)
	Frontal	–	2 (33.33)	3 (50)	1 (16.66)	6 (75)
	Temporal	–	1 (100)	–	–	1 (12.5)
	Parietal	–	1 (100)	–	–	1 (12.5)
	Total	4 (50)		4 (50)		8 (11.26)
	Age at onset	8.0 ± 6.29 (3–16)		7.5 ± 4.64 (1–11)		7.7 ± 5.2
	Duration of epilepsy	12.5 ± 7.71 (7–25)		12.5 ± 16.02 (5–41)		16 ± 11.7
	Age at surgery	23 ± 4.08 (18–28)		18.5 ± 19.12 (10–51)		23.7 ± 12.8

Table 6
Histopathological sub-classification of MRI and PET subgroups and correlations of MRI and PET subgroups with lesion localization.

	MRI-positive/PET-negative	MRI-positive/PET-negative	MRI-negative/PET-positive	MRI-negative/PET-negative
Type Ia	11 (28.20)	–	3 (30)	–
Type Ib	5 (12.82)	1 (10)	2 (20)	4 (50)
Type IIa	13 (33.33)	6 (60)	4 (40)	3 (37.5)
Type IIb	10 (25.64)	3 (30)	1 (10)	1 (12.5)
Temporal	18 (46.1)	4 (40)	5 (50)	1 (12.5)
Frontal	13(33.3)	4 (40)	2 (20)	4 (50)
Parietal	8 (20.5)	2 (20)	2 (20)	1(12.5)
Occipital	–	–	1 (12.5)	–
Total	39 (54.92)	10 (14.08)	10 (14.08)	8 (11.26)

surgery as adults [4]. A study that evaluated adults and children reported that the prevalence of FCD was 21% and that, other than hippocampal sclerosis, this disorder was the most common etiological factor associated with seizures [5]. In the same study, the age of seizure onset and age at surgery were younger and the seizure frequency was higher in patients with FCD compared with those with other etiologies. The present study also included both children and adult patients and found that the age of seizure onset was younger in PET-positive FCD patients relative to PET-negative patients.

Type I FCD is more often correlated with temporal lobe-based seizures, whereas type II FCD typically stems from damage in extratemporal regions and from multilobar and hemispheric cortical dysplasia that is localized in the frontal lobe [6,7]. The seizures of patients with type I FCD have a later age of onset, require surgery at more advanced ages, and are less frequent. In contrast, the seizures of type II FCD patients manifest during childhood, require surgery at early ages, and are more frequent [8–11]. In the present study, there were no significant differences in the PET or MRI findings or histopathological subgroups between the groups categorized by age at surgery or seizure onset. However, there was predominance of type II FCD in patients who developed seizures and underwent surgery prior to 18 years of age (Table 3).

According to MRI scans, the lesions tend to be wider in patients with an early age of onset for FCD [13]. Additionally, the age of seizure onset and age at surgery of patients with multilobar or hemispheric lesions for both type I and type II FCD are younger and the seizure duration of these groups is shorter [5,12]. These studies showed that, although the histopathological type of FCD and lesion size are factors that cause seizures at early ages, they are independent of each other [5]. In the present study, lesion size was not considered due to the limited number of patients and the variability in their results.

4.2. Evaluation of pre-operative MRI and PET results

MRI scans may not always reveal the presence of FCD. In their pioneering study, Taylor et al. [13] reported that a visible lesion was not present on the macroscopic examinations of six surgical samples, whereas another study found that MRI scans revealed all the lesions in type II FCD patients [14]. Moreover, previous studies identified lesions in 22% [5] and 4% [15] of patients, and most of these were type I FCD. In the present study, MRI scans revealed FCD in 74.65% of patients, and 64.15% of these patients were type II FCD. Although the difference was not statistically significant, the MRI scan was better able to reveal type II than type I FCD lesions. Of the MRI-negative patients, 50% were type I FCD and 50% were type II FCD. A review of the literature revealed that the post-operative histopathological examinations of MRI-negative patients showed mainly type I FCD (36%, 37%, and 85%), but they only rarely revealed type II FCD (2%, 15%, and 11%) [7,10,16,17]. In the present study, the MRI-negative patients showed a similar subgroup distribution [17].

Table 7
Comparison of four groups (MRI+/PET+, MRI+/PET−, MRI−/PET+, MRI−/PET−) based on outcomes.

	Good outcome		Poor outcome	
	Engel I	Engel II	Engel III + IV	Total
MRI+/PET+	33	4	2	39
MRI+/PET−	7	1	2	10
MRI−/PET+	10	–	–	10
MRI−/PET−	7	–	1	8

In the present study, the FCD lesions were localized in the temporal and frontal lobes in both the MRI-positive and MRI-negative patients, but there were no statistically significant differences between the groups in terms of histopathological sub-classification, lesion localization, or demographic variables. It is difficult to define the epileptogenic zone in MRI-negative patients, and PET scans may be used as another method of delineation that can provide additional information in this regard. Park et al. [18] found that the PET scans were positive in 92% of FCD patients, whereas Kim et al. [15] reported that the PET scans were positive in 69% (92/133) of patients. Similarly, Lerner et al. [5] reported that approximately 75% (181/242) of FCD patients had a positive PET scan.

In the present study, 74.6% of the patients were PET-positive, and 56.6% of these patients were type II (19 were IIa and 11 were IIb), whereas 43.4% were type I (14 were Ia and 9 were Ib). In terms of localization, the lesions were temporal in 23 patients, frontal in 17 patients, parietal in 10 patients, and occipital in 1 patient. In terms of the demographic characteristics of the PET-positive and PET-negative patients, the PET-positive patients had earlier ages of seizure onset ($p = 0.032$). Chugani et al. [19] reported that PET scans are more sensitive than are MRI scans for the determination of FCD in neonatal and infant subjects with focal seizures. More research is needed in this regard. In the present study, there were no differences between the PET-positive and PET-negative patients in terms of the duration of epilepsy or age at surgery.

4.3. Evaluation of MRI and PET findings by subgroup

An examination of the pre-operative assessments of the patients in the present study revealed that 39 were MRI-positive/PET-positive. Of these, 16 were type I FCD and 23 were type II FCD; the lesions were temporal in 18 patients, frontal in 13 patients, and parietal in 8 patients. Salamon et al. [17] found that 98% of patients were MRI-positive and that a significant portion of these patients were mild type I FCD with normal MRI scans. Additionally, previous studies have shown that 12 of 13 children with frontal lobe epilepsy (FLE) who were MRI-negative with micro-dyskinesia were PET-positive; [20] additionally, PET showed cortical hypometabolism in 7 of 9 FCD patients

(86%) with normal MRI scans [21]. Lerner et al. observed positive PET findings in 14 of 22 patients (64%) with normal or suspicious MRI findings [5].

Based on the findings of these studies, it is apparent that PET may be a very beneficial pre-operative examination technique for assessing refractory epilepsy patients, especially those with normal or suspicious MRI findings. In the present study, 10 of 18 patients (55.5%) with negative MRI findings also had positive PET findings. Of these cases, 50% had temporal localizations; half the patients were type I FCD, whereas the other half were type II FCD. Moreover, the demographic characteristics of these patients were similar. On the other hand, 90% of the MRI-positive/PET-negative patients were type II FCD (six were IIa and three were IIb). The histopathological subgroups, age at seizure onset, epilepsy times, and age at surgery of these MRI-positive/PET-negative were similar, and the possibility of having type II FCD was high.

Of the eight MRI-negative/PET-negative patients, 50% were type Ib FCD, 50% were type II FCD, and 75% had frontal localizations. However, there were no significant differences in terms of histopathological subgroups, lesion localization, or demographic variables. A review of the literature did not identify any studies that investigated this issue. The present study also evaluated the presence of lesions visible on MRI and PET scans. However, the size of the visible lesions and the degree of FDG uptake in the PET scans were not assessed, and these were limitations of this study.

In the present study, there were no correlations between histopathological subgroup of FCD and gender, age at seizure onset, duration of epilepsy, or age at surgery. PET scans reveal a lesion by showing hypometabolism in patients who have refractory epilepsy and an early age of onset. The present study suggests that the lesions of MRI-negative/PET-positive FCD patients tend to be localized in the temporal lobe and that FCD may be localized in the frontal lobe of MRI-negative/PET-negative patients. However, the histopathological examinations of MRI-positive/PET-positive, MRI-negative/PET-positive, and MRI-negative/PET-negative patients did not exhibit a particular histopathological subtype. In the present study showed all groups had very good outcome. There is no previous study concerning this issue in the literature.

In conclusion, structural imaging in conjunction with electrophysiological examinations may be useful for determining the epileptogenic zones of FCD patients, and these findings can be supported by FDG-PET findings. However, all types of FCD may be invisible despite the use of different imaging techniques, and this issue requires further investigation.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

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