

RESEARCH ARTICLE

A new perspective on drug-resistant epilepsy in children with focal cortical dysplasia type 1: From challenge to favorable outcome

Barbora Splitkova¹  | Katerina Mackova²  | Miroslav Koblizek³  |
 Zuzana Holubova⁴  | Martin Kyncl⁴  | Katerina Bukacova⁵  |
 Alice Maulisova⁵  | Barbora Straka¹  | Martin Kudr¹  | Matyas Ebel¹  |
 Alena Jahodova¹ | Anezka Belohlavkova¹  | Gonzalo Alonso Ramos Rivera⁶  |
 Martin Hermanovsky⁷  | Petr Liby⁸  | Michal Tichy⁸ | Josef Zamecnik³ |
 Radek Janca²  | Pavel Krsek¹ 

¹Department of Pediatric Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital, full member of the European Reference Network EpiCARE, Prague, Czech Republic

²Department of Circuit Theory, Faculty of Electrical Engineering, Czech Technical University in Prague, Prague, Czech Republic

³Department of Pathology and Molecular Medicine, Second Faculty of Medicine, Charles University and Motol University Hospital, full member of the European Reference Network EpiCARE, Prague, Czech Republic

⁴Department of Radiology, Second Faculty of Medicine, Charles University and Motol University Hospital, full member of the European Reference Network EpiCARE, Prague, Czech Republic

⁵Department of Clinical Psychology, Second Faculty of Medicine, Charles University and Motol University Hospital, full member of the European Reference Network EpiCARE, Prague, Czech Republic

⁶Department of Pediatrics, Martin University Hospital, Jessenius Faculty of Medicine in Martin, Martin, Slovak Republic

⁷Department of Water Resources and Environmental Modeling, Faculty of Environmental Sciences, Czech University of Life Sciences Prague, Prague, Czech Republic

⁸Department of Neurosurgery, Second Faculty of Medicine, Charles University and Motol University Hospital, full member of the European Reference Network EpiCARE, Prague, Czech Republic

Correspondence

Pavel Krsek, Department of Pediatric Neurology, Motol Epilepsy Center, Motol University Hospital, Second Faculty of Medicine, Charles University in Prague, Full Member of the ERN EpiCARE and Epilepsy Research Centre Prague–EpiReC consortium, V Uvalu 84, Prague 15006, Czech Republic.
 Email: pavel.krsek@fnmotol.cz

Abstract

Objective: We comprehensively characterized a large pediatric cohort with focal cortical dysplasia (FCD) type 1 to expand the phenotypic spectrum and to identify predictors of postsurgical outcomes.

Methods: We included pediatric patients with histopathological diagnosis of isolated FCD type 1 and at least 1 year of postsurgical follow-up. We systematically reanalyzed clinical, electrophysiological, and radiological features. The results of this reanalysis served as independent variables for subsequent statistical analyses of outcome predictors.

Barbora Splitkova and Katerina Mackova contributed equally as joint first authors.

Radek Janca and Pavel Krsek contributed equally as joint senior authors.

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Results: All children ($N=31$) had drug-resistant epilepsy with varying impacts on neurodevelopment and cognition (presurgical intelligence quotient [IQ]/developmental quotient scores = 32–106). Low presurgical IQ was associated with abnormal slow background electroencephalographic (EEG) activity and disrupted sleep architecture. Scalp EEG showed predominantly multiregional and often bilateral epileptiform activity. Advanced epilepsy magnetic resonance imaging (MRI) protocols identified FCD-specific features in 74.2% of patients (23/31), 17 of whom were initially evaluated as MRI-negative. In six of eight MRI-negative cases, fluorodeoxyglucose–positron emission tomography (PET) and subtraction ictal single photon emission computed tomography coregistered to MRI helped localize the dysplastic cortex. Sixteen patients (51.6%) underwent invasive EEG. By the last follow-up (median = 5 years, interquartile range = 3.3–9 years), seizure freedom was achieved in 71% of patients (22/31), including seven of eight MRI-negative patients. Antiseizure medications were reduced in 21 patients, with complete withdrawal in six. Seizure outcome was predicted by a combination of the following descriptors: age at epilepsy onset, epilepsy duration, long-term invasive EEG, and specific MRI and PET findings.

Significance: This study highlights the broad phenotypic spectrum of FCD type 1, which spans far beyond the narrow descriptions of previous studies. The applied multilayered presurgical approach helped localize the epileptogenic zone in many previously nonlesional cases, resulting in improved postsurgical seizure outcomes, which are more favorable than previously reported for FCD type 1 patients.

KEYWORDS

drug-resistant epilepsy, epilepsy surgery, focal cortical dysplasia type 1, multilayered diagnostic protocol, pediatric patients

1 | INTRODUCTION

Focal cortical dysplasia (FCD) is the most common cause of drug-resistant epilepsy (DRE) in children.^{1,2} FCD type 1 is still an enigmatic entity compared with FCD type 2, which has well-described neuroimaging³ and electrophysiological findings^{4–6} and genetic background.^{7–9}

More than 40% of patients with MRI-negative epilepsy indicated for resective epilepsy surgery have histopathologically confirmed FCD type 1.^{10–12} FCD type 1 lacks specific radiological hallmarks and does not show any characteristic interictal electroencephalographic (EEG) features on scalp EEG.¹³ However, a study¹⁴ recently described differences in some characteristics of interictal epileptiform discharges (IEDs) and repetitive discharges in intracranial EEG recordings between patients with FCD types 1 and 2.

Neurodevelopmental delay is a significant comorbidity in patients with FCD; approximately 53%–68% of patients have cognitive impairment.^{15,16} Patients with FCD

Key points

- The phenotypic spectrum of pediatric patients with FCD type 1 spans beyond the narrow description of previous studies.
- MRI-negative patients benefit from enhanced precision in localizing the epileptogenic zone, facilitated by FDG-PET, SISCOM, and SEEG.
- By applying a multilayered presurgical approach, surgical outcomes in patients with FCD type 1 are more favorable than previously reported.
- Pediatric patients with suspected FCD type 1 should be referred to epilepsy surgery centers as soon as possible.

1 have significantly lower developmental quotient/intelligence quotient (IQ) scores than those with FCD type 2.¹⁷ Other neuropsychological comorbidities, such as autism

spectrum disorder (ASD), are more likely to be associated with FCD type 1 than with FCD type 2.¹⁸ Cognitive decline in epilepsy is a common characteristic of FCD type 1.¹⁹ Because of the recurrent seizures and neuropsychological comorbidities, epilepsy has a devastating impact on quality of life in patients with FCD type 1.²⁰

Epilepsy surgery represents the only effective treatment for FCD type 1,²¹ but most studies have reported that the postsurgical seizure outcomes are significantly worse than those for FCD type 2²² or long-term epilepsy-associated tumors.²³ Previous studies have reported postsurgical seizure freedom in 21%²⁴ to 47%²⁵ of patients with FCD type 1.

This study comprehensively characterized the clinical phenotype of pediatric patients with isolated FCD type 1 to expand the understanding of the phenotypic spectrum of these patients. Additionally, we conducted a systematic reanalysis of electrophysiological and radiological features and outcomes and their predictors.

2 | MATERIALS AND METHODS

2.1 | Patient selection

This study involved a cohort of pediatric patients with focal DRE²⁶ who underwent resective or disconnective epilepsy surgery at Motol University Hospital in Prague between 2010 and January 2023. Included patients fulfilled the following criteria: (1) histopathological diagnosis of isolated FCD type 1 according to the latest International League Against Epilepsy (ILAE) classification²⁷ and (2) at least 1 year of postsurgical follow-up. Two expert neuropathologists (J.Z. and M.Ko.) re-evaluated all brain specimens to reach a consensus on FCD type 1 and its subtypes.

2.2 | Clinical history: Neurological and neuropsychological assessments

Individual patient characteristics obtained from electronic health records were retrospectively collected and reanalyzed with a focus on epilepsy phenotype and neuroimaging and electrophysiological features, which served as independent descriptors for subsequent statistical analyses. Epileptic seizures were classified according to the ILAE classification.²⁸ To characterize the time course of epilepsy, the following intervals were defined: (1) duration from epilepsy onset to epilepsy surgery and (2) duration from the first examination at our center to surgery.

Patients underwent neuropsychological assessment at the presurgical evaluation and 1 year after surgery. The following age-dependent tests were used: the Bayley Scale

of Infant and Toddler Development, 3rd edition²⁹; the Wechsler Preschool and Primary Scale of Intelligence, 4th edition³⁰; the Wechsler Intelligence Scale for Children, 3rd edition³¹; and the Wechsler Adult Intelligence Scale, 3rd edition.³²

2.3 | Electrophysiology

All patients underwent scalp video-EEG monitoring, encompassing wakefulness and sleep states for a minimum duration of 24 h; at least two habitual epileptic seizures were captured. A systematic reanalysis of the EEG characteristics³³ was conducted by P.K. with a focus on (1) background activity (primarily defined by frequency of the posterior dominant rhythm: normal or slow), (2) sleep architecture (normal or disrupted) and the presence of sleep spindles (symmetric, asymmetric, or absent), (3) local slowing (not present, regional, multiregional, hemispheric, or generalized), (4) the extent and localization of IEDs (not present, regional, multiregional, hemispheric, or generalized), (5) the presence of secondary bilateral synchrony (bilateral spread of IEDs), (6) the presence of EEG status epilepticus (continuous IEDs), and (7) the extent and localization of ictal activity (not lateralized, regional, multiregional, hemispheric, or generalized).

2.4 | Neuroimaging

All patients underwent high-resolution brain magnetic resonance imaging (MRI; 1.5 T or 3 T) using a dedicated epilepsy MRI protocol.³⁴ Two experienced pediatric neuroradiologists (M.Ku. and Z.H.) performed a systematic re-evaluation of all MRI studies, including consensus on the presence or absence of the following five radiological features defined in previous radiological studies on patients with FCD^{25,35–37}: (1) increased signal in the white matter on T2 and fluid-attenuated inversion recovery (FLAIR), (2) hypoplasia of the white matter, (3) blurring of the gray–white matter boundary (GWMB), (4) cortical thickening, and (5) abnormal gyral pattern. MRI findings were classified as focal, lobar, multilobar, or hemispheric, and the localization of the MRI abnormalities was specified. The specifications of the MRI protocols are provided in Table S2.

All patients underwent fluorodeoxyglucose positron emission tomography (FDG-PET) coregistered with MRI. For this study, images were reanalyzed and postprocessed by partial volume effect correction³⁸ to highlight cortical metabolic abnormalities, which were subjectively labeled as obvious hypometabolism, subtle or moderate hypometabolism, normal metabolism, and hypermetabolism,

and compared with resection: concordant, overlapped, partially overlapped, and discordant. In selected cases, ictal and interictal single photon emission computed tomography (SPECT) (99mTc-ethyl cysteinate dimer and subsequently 99mTc-hexamethylpropyleneamine oxime) had been performed and processed into subtraction ictal SPECT coregistered to MRI (SISCOM). The SISCOM findings were classified as focal, lobar, multilobar, or nonlocalized and compared with resection: concordant and discordant. A description of FDG-PET assessment is provided in Table S2.

All lesions and resection extents were manually outlined by Z.H. and K.M., respectively, in the preoperative MRI using 3D Slicer software and exported to binary label maps with voxels belonging to the lesion/resection (labeled 1) and background (labeled 0). The lesion/resection volumes were computed as the number of voxels (labeled 1) multiplied by the volume of an individual voxel. A detailed description of the volumetric analysis is provided in Table S1.

2.5 | Intracranial EEG

Long-term intracranial video-EEG monitoring (iEEG) was indicated if (1) the patient had nonlocalizing findings on MRI or discordant findings on noninvasive examinations or (2) the structural abnormality was adjacent to eloquent cortical areas. The implantation scheme of the depth (stereo-electroencephalography [SEEG]) electrodes (DIXI Medical) was planned with a neuronavigation system (StealthStation S7, Medtronic) for frame nonrobot Cosman–Roberts–Wells stereotaxy (Integra LifeSciences). Early cases ($n=2$) underwent implantation with subdural electrodes (Integra LifeSciences). Postimplantation computed tomography was fused with presurgical MRI to obtain recording contact positions related to brain anatomy.³⁹

2.6 | Epilepsy surgery, completeness of resection, and outcomes

The localization of the epileptogenic zone, estimated using seizure semiology and electrophysiological (iEEG and stimulation mapping) and neuroimaging (MRI, FDG-PET, and SISCOM) findings, was based on expert panel consensus. The completeness of resection was computed as the proportion of the MRI lesion volume included in the resection using the label maps of the outlined lesions. In MRI-negative/inconclusive cases, the completeness was determined by the proportion of iEEG channels within seizure onset that were included in the resection.

The completeness of hemispheric disconnection was evaluated by the analysis of postsurgical MRI and diffusion tensor imaging tractography.

Postsurgical seizure outcomes were assessed using the ILAE scale⁴⁰ with a 2-year follow-up (except for the last two cases, for which the follow-up was 1 year). Data regarding antiseizure medications (ASMs) were evaluated as follows: (1) a reduction in the number of ASMs (at least one ASM withdrawn), (2) complete discontinuation of ASMs, and (3) unchanged or modified without a significant reduction.

2.7 | Statistical analysis and modeling

Twenty-eight descriptors of clinical history, electrophysiological, neuroimaging, and neuropsychological findings, and seizure outcomes were selected to represent the patient cohort. Considering the limited sample size, descriptive statistics were predominately used to characterize the cohort. To complement the descriptive characteristics, stepwise generalized linear models (GLMs) with a binomial distribution and the logit link function were used to identify possible combinations of descriptors associated with favorable (ILAE class 1) or unfavorable (ILAE class 2–5) seizure outcomes. To reduce the model variance and eliminate the collinearity of model predictors, only a subset of descriptors was selected to build the GLMs. In cases of correlation or dependence ($p < .05$) between a pair of descriptors, only one representative descriptor with higher clinical importance was selected. Finally, the GLM was built using nine representative descriptors that met the selection criteria: age at epilepsy onset, resection completeness, resection volume, duration of epilepsy, ictal EEG pattern, performed iEEG monitoring, FDG-PET abnormalities, FDG-PET abnormalities and resection concordance, and MRI findings extent. The descriptor selection process revealed dependencies between descriptors, some of which are reported in the text. Further details are provided in Data S1. All analyses were performed with MATLAB software (version 2023b, MathWorks). The median values are reported together with the interquartile range.

3 | RESULTS

3.1 | Clinical characterization

We enrolled 31 pediatric patients (17 females and 14 males); 27 patients (87.1%) had histopathologically confirmed FCD type 1A, and four patients (12.9%) had FCD type 1C. The basic clinical characteristics are

summarized in Table 1; details are provided in Table S1. None of the children had febrile seizures. Three patients (9.7%) had a family history of epilepsy (first or second degree). Ten patients (32.3%) exhibited abnormal focal or nonfocal neurological findings (such as hypotonia). Six patients (19.4%) had perinatal complications (e.g., prematurity, defined by the World Health Organization as any birth before 37 weeks of gestation or a low Apgar score [<7] at any time point) without neuroradiological abnormalities suggestive of perinatally acquired brain lesions. Developmental delay before epilepsy onset was noted in five patients (16.1%). In 25 patients (80.6%), developmental arrest, regression, or cognitive decline was observed during the course of epilepsy.

The median age at epilepsy onset was 4.2 years (.9–8.5 years), and 15 patients (48.4%) had epilepsy onset before the age of 3 years. Daily seizures were reported in 27 patients (77.4%). The median age at the first examination at the Motol Epilepsy Center was 8.0 years (3.3–13.2 years). The median duration from epilepsy onset to referral to the epilepsy center was 2.3 years (1.5–3.5 years). Various types of focal seizures were reported in 27 patients (87.1%), and epileptic spasms were reported in seven individuals (22.6%). Sixteen patients (51.6%) experienced focal to bilateral tonic-clonic seizures. Additionally, four patients (12.9%) had episodes of status epilepticus. All patients developed drug resistance; the median number of tested ASMs was 6^{4–8} and median number of ASMs at the time of surgery was 2.^{2,3} Fifteen patients (48.4%) experienced a period of temporary seizure freedom (defined in this study as a minimum of 3 months without experiencing seizures).

3.2 | Electrophysiological characterization

The main electrophysiological features observed in our cohort are summarized in Table 2. Background EEG activity was normal in 17 patients (54.8%). Disrupted sleep architecture was noted in 16 patients (51.6%), and nine patients (29.0%) exhibited asymmetry or absence of sleep spindles. Localized EEG slowing was regional in seven patients (22.6%), multiregional in 16 (51.6%), hemispheric in four (12.9%), and generalized in three (9.7%), and one patient showed no localized slowing. Localized EEG slowing was intermittent in 19 patients (60.0%) and continuous in 12 patients (40.0%). Interictal EEG spikes were predominantly multiregional and were noted in 20 individuals (64.5%), with the maximum over the temporal or fronto-temporal regions. Ictal EEG patterns were multiregional in 13 patients (41.9%), regional in eight (25.8%), generalized in four (12.9%), hemispheric in three (9.7%), and not

lateralized in three (9.7%). Secondary bilateral synchrony was noted in 13 patients (41.9%). Patients with disrupted sleep architecture had larger resection volumes than those with normal sleep architecture ($p=.05$, Kruskal–Wallis; 49 cm³ [37–84] vs. 28 cm³ [22–45]). Patients with more extensive structural abnormality on MRI tended to have slow background activity ($p=.02$, chi-squared test). We observed a trend of earlier epilepsy onset in patients with slow background activity compared to those with normal background activity ($p=.13$, Kruskal–Wallis; 2.3 years [1.5–4.7] vs. 6 years [1.1–10.3]).

3.3 | Neuropsychological characterization

Presurgical IQ scores were available for 28 of 31 patients; the median score was 76 (64–87) points, and IQ scores ≥ 80 were observed in 12 of 28 (42.6%) patients. The descriptor selection process revealed trends related to neuropsychological characterization. There was a high correlation between pre- and postsurgical IQ scores ($r=.87$, $p<.001$, Spearman correlation). Lower presurgical scores were correlated with an earlier age at epilepsy onset ($r=.4$, $p=.03$, Spearman correlation). Patients with normal sleep architecture ($n=16$) had higher presurgical IQ scores than those with disrupted sleep architecture ($n=12$; $p=.04$, Kruskal–Wallis; 84 [75–97] vs. 68 [50–85]). Similarly, patients ($n=17$) with normal background EEG activity had higher IQ scores than patients with slow background EEG activity ($n=11$; $p=.02$, Kruskal–Wallis; 85 [75–91] vs. 64 [50–78]). A trend of larger resection volumes in patients with lower presurgical IQ scores was observed ($r=-.32$, $p=.12$, Spearman correlation).

Among other neuropsychological comorbidities, two patients had attention-deficit/hyperactivity disorder and three patients had ASD, one of whom had Asperger syndrome.

3.4 | Neuroimaging characterization

Twenty-three patients (74.2%) had visible MRI abnormalities, whereas eight patients (25.8%) displayed no signs of malformation of cortical development. Initial MRI (taken and evaluated out of our center) was reported as normal or abnormal without signs of FCD (e.g., nonspecific gliosis) in 24 patients (77.4%), but MRI performed with a dedicated epilepsy protocol at our center revealed signs of FCD in 17 of 24 initially negative patients (70.8%). The left hemisphere was affected in 14 patients who were MRI-positive (60.9%). Table 3 summarizes the radiological features observed in our cohort.

TABLE 1 Clinical characterization.

ID	Sex	Age at 1st seizure, years	DD before epilepsy onset	Neurological findings	Focal seizures	FBTCS	Spasms	Seizure frequency	ASMs	Seizure-free period	Duration of epilepsy, years
Seizure-free											
1	F	0.5	+	NF	—	—	+	D	5	—	2.7
2	F	0.5	—	N	—	—	+	D	6	+	1.4
3	F	8.2	—	F, NF	+	+	—	D	6	—	2.3
4	F	0.2	+	N	+	+	—	D	4	+	7.2
5	F	6.0	—	N	+	+	—	W	6	+	4.5
6	F	0.3	—	F, NF	+	—	+	D	9	+	2.7
7	F	0.4	—	N	+	—	—	D	4	—	4.3
8	F	0.7	—	N	+	—	+	D	9	+	4.0
9	M	1.0	—	N	+	+	—	W	2	+	1.0
10	F	1.2	—	NF	+	—	+	D	4	—	2.6
11	M	1.2	—	F, NF	+	—	—	M	4	+	3.1
12	M	1.2	—	N	+	+	—	M	8	+	16.7
13	M	2.0	—	N	+	+	—	W	7	+	7.3
14	M	2.5	—	NF	+	—	—	D	10	—	4.0
15	F	4.3	—	N	+	+	—	D	4	—	4.2
16	F	4.7	—	F, NF	+	—	—	D	11	+	5.8
17	M	6.0	—	F	+	—	—	W	10	—	2.8
18	M	8.6	+	N	+	+	—	D	6	+	3.2
19	F	10.0	—	N	+	—	—	D	9	—	6.4
20	M	11.0	—	N	+	+	—	D	6	—	3.4
21	M	10.0	—	N	+	+	—	D	4	+	4.0
22	F	4.2	—	N	—	—	+	D	5	—	1.3
Non-seizure-free											
23	F	12.8	—	N	+	+	—	W	5	—	5.2
24	M	14.0	—	N	+	+	—	W	2	—	2.3
25	F	11.0	+	N	+	+	—	D	4	—	3.3
26	F	16.0	—	N	+	+	—	D	6	—	2.6
27	M	0.4	—	N	—	—	+	D	9	—	1.1
28	M	8.4	—	N	+	+	—	D	4	—	2.2
29	M	0.3	+	NF	+	—	—	D	6	+	3.9
30	M	2.2	—	F	+	+	—	D	7	+	17.8
31	F	5.5	—	N	+	—	—	D	8	+	4.4

Note: Sex: F, female; M, male. Neurological findings: N, normal; F, focal; NF, nonfocal. Seizure frequency: D, daily; M, monthly; W, weekly. Intracranial EEG: S, stereoelectroencephalography; E, ECoG. Surgery extent: F, focal; H, hemispherotomy; L, lobar; M, multilobar. Surgery extent—specification: F, frontal; C, central; I, opercularinsular; O, occipital; P, parietal; T, temporal.

Abbreviations: —, no/negative/not available; +, yes/positive; DD, developmental delay; EcoG, electrocorticography; EEG, electroencephalography; FBTCS, focal to bilateral tonic-clonic seizures; ID, patient identifier; ILAE, International League Against Epilepsy; IQ, intelligence quotient.

The most common radiological features observed in the MRI-positive subgroup were an increased white matter signal in T2W and FLAIR sequences (95.7%), hypoplasia of the white matter (87.0%), and blurred gray-white matter junction (82.6%). Cortical thickening (47.8%) and abnormal

gyral patterns (47.8%) were less common. The extent of MRI findings was lobar in 11 patients (47.8%), multilobar in 11 cases (47.8%), and hemispheric in one case (4.3%).

SISCOM was conducted in 18 patients (58.1%) with focal ($n=1$), lobar ($n=5$), multilobar ($n=6$), and

Intracranial EEG	Surgery extent	Surgery extent—specification	Intraoperative EcoG	Outcome, ILAE class	Reduced ASM	Drug-free	IQ score, presurgical	IQ score, 1 year after surgery
—	H	—	—	1	+	—	32	—
—	L	T	+	1	+	—	—	55
S	H	—	—	1	+	—	76	71
—	L	T	+	1	+	+	47	—
E	M	T, P	+	1	+	—	82	81
—	H	—	—	1	+	—	50	57
S	F	I	+	1	+	—	88	65
—	M	F, T	+	1	+	+	56	59
—	L	T	+	1	+	+	85	91
—	L	F, T	+	1	+	—	67	56
S	L	P	+	1	+	+	85	84
S	L	T	+	1	+	—	97	93
S	F	I	+	1	—	—	76	—
S	F	I	+	1	+	—	63	61
—	L	T	+	1	+	—	106	110
S	M	F, C, P	+	1	+	—	49	57
S	M	P, O	+	1	+	—	85	68
S	F	P	+	1	+	—	79	97
S, E	M	F, T	+	1	+	—	74	69
S	M	T, P, O	+	1	+	+	92	94
S	L	T	+	1	—	—	—	—
—	M	F, T	+	1	—	—	64	—
—	F	T	+	3	+	—	86	106
—	F	T	+	3	+	—	—	—
—	L	T	+	4	—	—	68	60
S	M	T, I	+	4	—	—	105	94
—	F	P	+	4	—	—	105	—
S	F	F, I	+	4	—	—	99	102
—	M	F, T	+	5	—	—	43	21
—	L	T	+	5	—	—	69	—
S	F	F	+	5	—	—	75	85

nonlocalized ($n=6$) findings. The SISCOM finding was concordant with the resection in 10 of the 18 patients (56%) and discordant in eight of the 18 patients (44%). All 31 patients in the study underwent FDG-PET. An obvious hypometabolism on FDG-PET was observed in 17

patients (54.8%), whereas a subtle or moderate hypometabolism was observed in eight patients (25.8%). Three patients (9.7%) had normal metabolism on FDG-PET. Localized hypermetabolism was observed in three individuals (9.7%), possibly because these patients had almost

TABLE 2 Electrophysiological characterization.

ID	Background activity	Sleep spindles	Sleep architecture	EEG slowing	Presence of EEG slowing	Interictal EEG spikes	Secondary bilateral synchrony	Maximum of the interictal activity	Ictal EEG pattern	Maximum of the ictal epileptiform pattern
Seizure-free										
1	S	Absent	D	G	C	M	+	TPO right	G	–
2	S	Asymmetric	D	M	C	M	+	FCTP left	G	Left
3	N	Asymmetric	D	M	C	M	+	FCP right	M	FCP right
4	S	Symmetric	D	R	C	R	+	T left	R	T left
5	N	Symmetric	N	M	I	M	+	CTPO right	M	CTP right
6	S	Asymmetric	D	G	C	H	+	F left	R	F left
7	N	Symmetric	N	R	I	R	–	FT right	R	FT right
8	N	Symmetric	D	M	I	M	+	FT right	G	FT right
9	N	Symmetric	N	R	I	R	+	T left	R	T left
10	S	Symmetric	D	M	C	H	+	FT left	H	T left
11	N	Absent	D	M	I	M	+	FCP right	M	FCP right
12	N	Symmetric	N	R	I	R	+	T left	R	T left
13	S	Symmetric	N	M	I	M	+	FT right	M	FT right
14	S	Symmetric	N	M	I	M	–	FT left	M	FT left
15	S	Symmetric	N	R	I	R	–	T left	R	T left
16	S	Asymmetric	D	H	C	M	–	CP left	H	CP left
17	S	Symmetric	D	M	C	M	+	TPO left	NL	Middle
18	N	Symmetric	N	M	I	H	–	CTP left	H	FCTP left
19	S	Asymmetric	D	M	I	M	+	CT right	M	CT right
20	N	Symmetric	D	H	I	M	+	T left	M	FT left
21	N	Asymmetric	D	M	I	M	–	FT right	M	FT right
22	S	Symmetric	D	G	C	NL	+	FT right	G	NL
Non-seizure-free										
23	N	Symmetric	N	R	I	R	–	T left	R	T left
24	N	Symmetric	N	–	–	–	–	–	R	T left
25	N	–	D	H	I	M	–	FTP right	M	FTP right
26	S	Symmetric	N	M	I	M	+	T left	NL	NL
27	N	Symmetric	N	H	C	M	–	TP left	M	TP left
28	N	Asymmetric	D	M	C	M	–	FT left	M	FT left

TABLE 2 (Continued)

ID	Background activity	Sleep spindles	Sleep architecture	EEG slowing	Presence of EEG slowing	Interictal EEG spikes	Secondary bilateral synchrony	Maximum of the interictal activity	Ictal EEG pattern	Maximum of the ictal epileptiform pattern
29	S	Symmetric	N	M	I	M	–	FT left	M	NL
30	N	Symmetric	N	R	I	M	+	T left	NL	NL
31	N	Symmetric	N	M	C	M	+	FCP right	M	FCP right

Note: Maximum of the interictal activity, Maximum of the ictal epileptiform pattern—specification: F, frontal; C, central; O, occipital; P, parietal; T, temporal. Abbreviations: –, no/not available; +, yes; C, continuous; D, disrupted; EEG, electroencephalographic; G, generalized; H, hemispheric; I, intermittent; ID, patient identifier; M, multiregional; N, normal; NL, not lateralized; R, regional; S, slow.

continuous interictal epileptiform discharges at the time of the FDG-PET examination. The identified abnormal region was concordant with the resection in eight patients (25.8%), overlapped with the resection in four patients (12.9%), and partially overlapped in 14 patients (45.2%). In the MRI-negative subgroup ($n=8$), a combination of FDG-PET and SISCOM helped localize the epileptogenic zone in six of the eight patients (75.0%). Only one patient had nonlocalized FDG-PET and SISCOM.

3.5 | Epilepsy surgery and completeness of resection

The median age at epilepsy surgery was 9.3 years (4.3–14.2 years), and the median duration of epilepsy was 3.4 years (2.6–4.5 years). The median duration from the first examination at our center to epilepsy surgery was 11 months (7–14 months). Sixteen patients (51.6%) underwent long-term iEEG monitoring before epilepsy surgery; half of them were MRI-negative. Twenty-eight patients (90.3%) underwent resective surgery. The extent of resection was focal (sublobar) in eight patients (25.8%), lobar in 10 patients (32.3%), and multilobar in 10 patients (32.3%). Three patients (9.7%) underwent hemispheric disconnection. Reoperation was necessary in one patient, and two patients underwent implantation of vagus nerve stimulator.

The median volume of resection (excluding hemispherectomy) was 38 cm³ (24–73 cm³), and the resection extent was similar in MRI-lesional and MRI-negative groups. The median completeness of lesion resection as assessed with MRI was 77.0% (73%–95%); the completeness of resection as assessed with iEEG was 88.2% (79%–98%). Complete hemispheric disconnection was achieved in all three patients.

The multimodal approach resulting in resective surgery in selected cases is illustrated in Figure 1.

3.6 | Outcomes and analysis of their predictors

By the last follow-up, 22 patients (71.0%) had achieved seizure freedom (ILAE class 1). Two patients (6.5%) were classified as ILAE class 3, four patients (12.9%) were classified as ILAE class 4, and three patients (9.7%) were classified as ILAE class 5. Notably, in the MRI-negative subgroup, seven of the eight patients (87.5%) achieved long-term seizure freedom. The median follow-up period was 5 years (3.3–9). The seizure outcome was similar in the MRI-negative and MRI-positive groups ($p=.23$, chi-squared test). ASMs were reduced in 21 patients (67.7%),

TABLE 3 Radiological characterization.

ID	FCD MRI findings	Increased T2W FLAIR signal	White matter hypoplasia	GWMB	Abnormal cortical thickening	Abnormal gyral pattern	Number of features	Side
Seizure-free								
1	+	+	+	+	—	—	3	R
2	+	+	—	—	—	—	1	L
3	—	—	—	—	—	—		
4	+	+	+	+	+	—	4	L
5	—	—	—	—	—	—		
6	+	+	+	+	—	+	4	L
7	—	—	—	—	—	—		
8	+	+	+	+	+	+	5	R
9	+	+	+	—	—	—	2	L
10	+	+	+	+	—	—	3	L
11	+	—	+	—	—	+	2	R
12	—	—	—	—	—	—		
13	+	+	—	+	—	+	3	R
14	+	+	+	+	—	—	3	L
15	+	+	—	+	+	+	4	L
16	—	—	—	—	—	—		
17	+	+	+	—	—	—	2	R
18	+	+	+	+	+	+	5	L
19	+	+	+	+	+	+	5	R
20	—	—	—	—	—	—		
21	—	—	—	—	—	—		
22	+	+	+	+	+	—	4	R
Non-seizure-free								
23	+	+	+	+	—	—	3	L
24	+	+	+	+	+	+	5	L
25	+	+	+	+	—	—	3	R
26	+	+	+	+	—	—	3	L
27	+	+	+	+	+	+	5	L
28	+	+	+	+	+	+	5	L
29	+	+	+	+	+	+	5	L
30	+	+	+	+	+	—	4	R
31	—	—	—	—	—	—		

Abbreviations: —, no/not available; +, yes; amg, amygdala; C, concordant; D, discordant; f, focal; F, frontal; FCD, focal cortical dysplasia; GWMB, blurring of the gray–white matter boundary; H, hemispheric, hip, hippocampus; Hy, hypometabolic; HY, hypermetabolic; I, insula; ID, patient identifier; L, left; Lo, lobar; M, multilobar; MH, moderate hypometabolic; MRI, magnetic resonance imaging; NL, nonlocalized; O, occipital; OV, overlapped; P, parietal; PA, partial; PET, positron emission tomography; R, right; SISCOM, subtraction ictal SPECT coregistered to MRI; SPECT, single photon emission computed tomography; T, temporal; T2W, T2-weighted.

and complete withdrawal of ASMs was possible in six individuals (19.4%). Patients with regional ictal EEG patterns had a better chance of reducing ASMs ($p = .04$, chi-squared test).

Neuropsychological profiles before surgery and after 1 year of follow-up were available in 24 patients (77.4%).

The median postsurgical IQ score was 71 (60–94) points. We did not observe a correlation between a postsurgical increase or decrease in IQ and seizure outcomes. Three patients exhibited an increase in IQ score of >10 points (one was seizure-free, one was in ILAE class 3, and one was in class 5), and three exhibited a decrease in IQ score

Extent of MRI abnormalities	Lobar distribution	SPECT	Extent of SISCOM findings	SISCOM and resection	PET	PET abnormalities	PET and resection
H	Hy	—			+	MH	PA
Lo	T	—			+	H	C
		—			+	HY	PA
M	TI	+	Lo	+	+	H	OV
		+	M	+	+	MH	PA
M	FTI	—			+	H	C
		+	f	+	+	H	PA
M	FTIP	+	L	+	+	H	PA
M	TI	—			+	H	C
M	FT	+	Lo	+	+	MH	D
Lo	P	+	M	+	+	HY	C
		+	NL	—	+	MH	D
Lo	FI	+	NL	—	+	MH	C
M	TI	—			+	H	OV
Lo	T	+	L	—	+	H	OV
		+	NL	—	+	H	C
M	PO	+	M	+	+	H	PA
Lo	P	+	NL	—	+	H	C
Lo	F	+	M	+	+	H	PA
		+	M	+	+	HY	PA
		+	M	—	+	MH	PA
M	FTI	—			+	H	C
Lo	T (amg)	—			+	MH	PA
Lo	T	—			+	—	D
Lo	T (amg, hip)	—			+	H	PA
M	IT (amg)	+	NL	—	+	MH	PA
Lo	P	—			+	—	D
M	FTI	—			+	H	OV
M	FTI	—			+	H	PA
Lo	T	+	Lo	+	+	H	PA
		+	NL	—	+	—	D

of >15 points (two were seizure-free; one was in ILAE class 5).

Seizure outcome class was predicted by a GLM with a combination of the following descriptors: age at epilepsy onset (A), epilepsy duration (D), performance of iEEG exploration (I), extent of MRI (M), and PET (P) findings.

The resulting GLM model was as follows: $\text{logit (ILAE class)} = 1.63 - .05A - .03D + 2.61 + 3.28P - 2.34M$; $p < .003$. The 95% confidence intervals for the coefficient estimates were -4.557 to 7.811 for the intercept, $-.108$ to $.002$ for A, $-.065$ to $.005$ for D, $-.748$ to 5.938 for I, $.088$ to 6.462 for P, and -5.497 to $.824$ for M. This model suggests that earlier

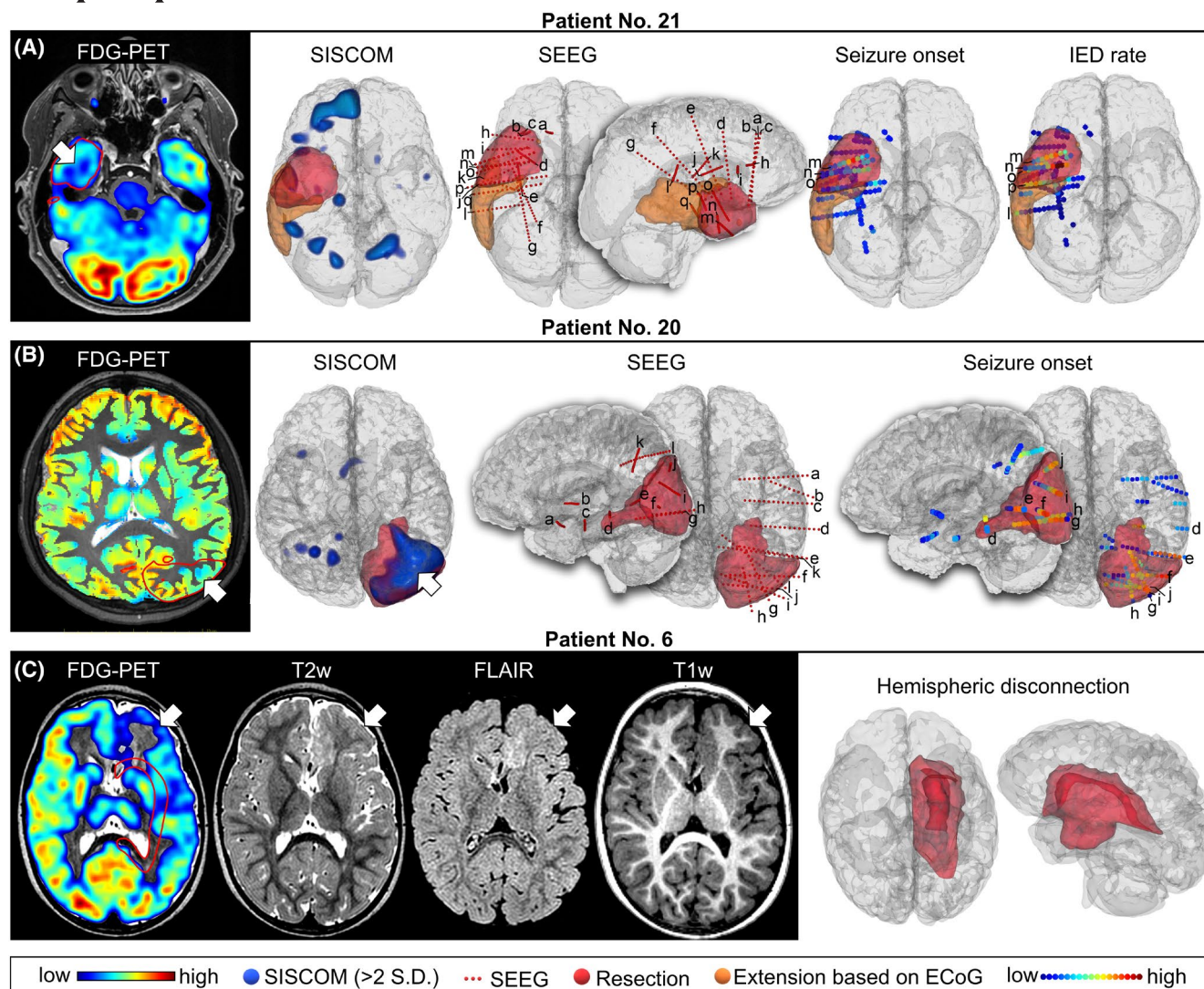


FIGURE 1 An example of the importance of multimodal assessment in three postoperative seizure-free patients. (A) Patient 21 had normal magnetic resonance imaging (MRI) findings and lateralizing but nonlocalizing single photon emission computed tomography coregistered to MRI (SISCOM). Scalp electroencephalography (EEG) showed extensive frontotemporal epileptiform activity on the right. Fluorodeoxyglucose positron emission tomography (FDG-PET) with additional postprocessing revealed a mild hypometabolism on the base of the temporal pole (arrow), which was the target of stereoelectroencephalographic (SEEG) exploration of frontal (a–c, j, k), insular (d–i), temporal (m–q) lobes, and Rolandic operculum (l). Seizure onset zones⁴¹ were confirmed in the hypometabolic tissue. However, interictal epileptiform discharges (IEDs) were widespread in the temporal lobe, indicating an extensive epileptic network⁴². The initial resection plan (red area) was extended intraoperatively on the basis of electrocorticography (ECoG; orange area) including the region uncovered by SEEG electrodes. The patient was completely seizure-free during follow-up. (B) Patient 20 had normal MRI findings with subtle hypometabolic abnormalities in FDG-PET on left parieto-occipital lobes (arrow) and multilobar left frontotemporal EEG findings. SISCOM localized the epileptogenic zone to the left temporoparieto-occipital region (arrow), which was confirmed by SEEG exploration of temporal (a–e, g), occipital (f–j), and parietal (k, l) lobes. (C) Patient 6 (an infant) had extensive left-sided structural abnormalities visible on MRI in the frontoinsular-temporal region with the corresponding FDG-PET hypometabolism (arrows). The patient underwent a left hemispherectomy. T1w, T1-weighted; FLAIR, fluid-attenuated inversion recovery.

epilepsy onset is associated with a higher probability of a favorable outcome, and iEEG monitoring increased this probability in patients with late epilepsy onset. Shorter epilepsy duration, less extensive MRI, and clearly visible PET abnormalities increased the probability of seizure freedom. The detailed results are provided in Data S1.

3.7 | Long-term experience at Motol Epilepsy Center

The descriptor selection process revealed interesting trends related to long-term experience at Motol Epilepsy Center. Although the resection volume decreased with

time ($r = -.54$, $p < .003$, Spearman correlation), the resection completeness improved ($r = .41$, $p = .03$, Spearman correlation). The duration of epilepsy decreased with time ($r = -.41$, $p = .02$, Spearman correlation), whereas the duration from the first examination at our center to epilepsy surgery remained the same. The effect of the year of surgery on the seizure outcome was not observed. Twenty patients (64.0%), including seven of the eight patients in the MRI-negative subgroup (88.0%), were indicated for epilepsy surgery after 2017.

4 | DISCUSSION

FCD type 1 is one of the most challenging causes of focal DRE in surgical cohorts; it is always associated with the terms “difficult to diagnose” or “difficult to treat.” To the best of our knowledge, this study presents the largest single-center cohort of pediatric patients with histopathologically confirmed FCD type 1, comprising 31 children. We focused on reanalyzing electroradiological characteristics, describing clinical features in detail, and analyzing outcome predictors.

Our data suggest extreme phenotypic variability, expanding the classical phenotype of FCD type 1 patients described by Holthausen and colleagues^{13,24} with the characteristic of age at epilepsy onset in infancy or early childhood. Despite the predominance of FCD type 1A in our cohort, the clinical phenotype does not completely overlap with the recently described disease multilobar unilateral hypoplasia with severe epilepsy in children (MUHSEC), which is characterized by early onset DRE, severe mental retardation, and characteristic electrophysiological and neuropathological findings.²⁵ The age at epilepsy onset in our cohort was highly variable, and these results are concordant with the findings reported by Yao et al.⁴³ and Guerrini and Barba.⁴⁴ None of our patients exhibited neonatal seizures or epilepsy onset in the first 2 months of life; this is comparable to MUHSEC and differs from extensive FCD type 2.⁴⁰ Most patients in our study experienced daily seizures, similar to patients with MUHSEC; however, some patients experienced weekly or monthly seizures, similar to patients in a recent study.²² The median duration of epilepsy in our study was 3.4 years, which is slightly below the duration reported in a large European multicenter epilepsy surgery series.⁴⁵ We observed a shorter duration of epilepsy in patients who underwent surgery in later years. We believe that this is a result of nationwide education, which shortened the time until referral to an epilepsy center.

We observed a negative impact of ongoing epilepsy on children's development and cognition in most of our cases, consistent with previous studies.^{15,16} Limited

evidence indicates that focal epilepsy disrupts the structure and function of sleep spindles, which may play a role in impaired cognitive functioning.⁴⁶ However, we did not observe a difference in presurgical IQ scores between patients with asymmetric or absent and symmetric sleep spindles. Interestingly, larger resection volumes were observed in patients with lower presurgical IQ and those with disrupted sleep architecture. Additionally, slow background EEG activity was linked to lower presurgical IQ scores. This suggests that the structural abnormality itself together with extensive epileptiform activity contributes to abnormalities in sleep microarchitecture and background activity, thereby affecting cognitive and behavioral functioning beyond the direct impact of seizures.⁴⁷ We did not observe a significant difference between presurgical and postsurgical IQ scores, possibly because of the short follow-up period, which also did not allow, for example, analysis of the effect of ASM withdrawal. However, our observations also indicate that patients with earlier epilepsy onset tended to have lower presurgical IQ scores.

Interictal and ictal EEG findings frequently suggested multiregional epileptiform activity with predominance over the temporal, frontal, and parietal regions and a tendency toward generalization, as evidenced by the phenomenon of secondary bilateral synchrony. Inconsistent with MUHSEC, no patients showed posterior predominance. Extensive epileptiform activity was observed not only in patients with multilobar MRI abnormalities but also in those with lobar distribution and normal MRI findings. These observations suggest that scalp EEG has limited localization value; thus, more advanced techniques, especially neuroimaging, are required. In contrast to FCD type 2, which is characterized by focal rhythmic epileptiform discharges,⁴ we did not detect any distinctive EEG features in FCD type 1.

Approximately 60% of patients with FCD type 1 have visible MRI abnormalities.⁴⁸ However, the utilization of MRI protocols for epilepsy enabled the identification of FCD-related abnormalities in many of our patients (74.2% of cases). Moreover, the advanced MRI protocols provided at our epilepsy center revealed FCD features in 70.8% of patients who were classified as MRI-negative when referred to our center. We observed increased white matter signal intensity in the T2W and FLAIR sequences and hypoplasia of the white matter, which are MRI hallmarks of MUHSEC; additionally, a blurred gray-white matter junction was a frequent feature in our cohort, but this is rare in MUHSEC.²⁵ The distribution of MRI abnormalities was mainly multilobar or lobar, with predominance in the temporal, frontal, and insular lobes. In MRI-negative patients and cases with visible lesions not corresponding to the distribution of

epileptiform activity on EEG, additional neuroimaging techniques, such as FDG-PET and SISCOM, can be highly beneficial. Using these examinations, we were able to localize the presumed epileptogenic zone in six of the eight MRI-negative patients. Advances in neuroimaging and the growing experience of our team resulted in an increased number of candidates with FCD type 1 identified for surgical treatment. Two thirds of patients in our cohort (including most MRI-negative patients) underwent surgery in the second half of the study period (2017–2023).

Surgical resection or disconnection procedures successfully eliminated seizures (ILAE class 1) in 71% of the children. These outcomes are more favorable than those reported in previous studies involving patients with FCD type 1^{22,24,25,49} and are more similar to the postsurgical outcomes of patients with FCD type 2.²² Notably, MRI-negative patients had excellent seizure outcomes and undoubtedly benefited from enhanced precision in localizing the epileptogenic zone facilitated by FDG-PET, SISCOM, and SEEG. Moreover, we observed trends of decreasing resection volume and improving resection completeness in later indicated patients. Analysis of outcome predictors suggests that earlier epilepsy onset, shorter epilepsy duration, less extensive MRI, clearly visible PET abnormalities, and performed iEEG exploration increased the chance of seizure freedom.

Our study has certain limitations. Most importantly, the histopathological evaluation of FCD type 1 specimens is subject to bias, with significant interobserver variability even among expert neuropathologists.⁵⁰ To mitigate this, only patients with representative brain tissue samples were included, and all histopathology samples underwent a systematic review by two neuropathologists with long-term expertise in malformations of cortical development. Conversely, we were able to exclude patients with a diagnosis of mild malformation of cortical development and oligodendroglial hyperplasia and epilepsy (MOGHE) based on histopathological characteristics and the presence of somatic pathogenic variants in the *SLC35A2* gene. Additionally, given the enigmatic nature of the genetic causes of FCD type 1, we currently lack a gene-based diagnostic approach. Genetic factors likely influence seizure outcomes, cognitive development, and the general phenotype in patients with FCD type 1, and several studies have attempted to elucidate its genetic background. However, no specific gene variants or chromosomal loci have been conclusively linked to FCD type 1.⁵¹ Another potential limitation could be the size of our cohort; however, given the rareness of FCD type 1, our cohort represents one of the largest and best characterized ones yet published.

5 | CONCLUSIONS

Previous studies^{22,24,25,49} have reported unfavorable seizure outcomes in patients with FCD type 1. Our study provides evidence to the contrary; patients with FCD type 1 benefited from epilepsy surgery when it was performed after a complex multimodal presurgical diagnostic process capable of delineating the precise extent of the epileptogenic zone. The phenotypic spectrum of patients with FCD type 1 spans beyond the narrow description of MUHSEC²⁵ and classical FCD type 1 described by Holthausen and colleagues^{13,24} with varying cognitive and developmental levels, albeit with the universal presence of DRE. We recommend that patients with DRE with suspected FCD type 1 be referred to epilepsy surgery centers as early as possible.

AUTHOR CONTRIBUTIONS

Barbora Splitkova and Pavel Krsek were involved in conceptualization, investigation, data curation, and writing—original draft preparation. Radek Janca and Katerina Mackova were involved in conceptualization and writing—original draft preparation. Barbora Straka was involved in writing—review & editing. Martin Kudr, Matyas Ebel, Alena Jahodova, Anezka Belohlavkova, Gonzalo Alonso Ramos Rivera, Katerina Bukacova, Alice Maulisova, Miroslav Koblizek, Josef Zamecnik, Zuzana Holubova, Martin Kyncl, Petr Liby, Michal Tichy, and Martin Hermanovsky were involved in resources.

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CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the institutional ethical committee of Motol University Hospital (2022/06/15-EK-602.24/22). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Barbora Splitkova  <https://orcid.org/0000-0002-3462-7421>

Katerina Mackova  <https://orcid.org/0000-0001-8568-0006>

Miroslav Koblízek  <https://orcid.org/0000-0002-8422-732X>

Zuzana Holubova  <https://orcid.org/0009-0000-4046-4473>


Martin Kyncl  <https://orcid.org/0000-0001-6210-6351>

Katerina Bukacova  <https://orcid.org/0000-0002-6124-1583>

Alice Maulisova  <https://orcid.org/0000-0001-7026-8238>

Barbora Straka  <https://orcid.org/0000-0001-8448-2833>

Martin Kudr  <https://orcid.org/0000-0001-7853-3446>


Matyas Ebel  <https://orcid.org/0000-0002-4795-152X>

Anezka Belohlavkova  <https://orcid.org/0000-0001-8462-6892>

Gonzalo Alonso Ramos Rivera  <https://orcid.org/0009-0003-4184-0321>

Martin Hermanovsky  <https://orcid.org/0000-0002-8355-9840>

Petr Liby  <https://orcid.org/0000-0001-8392-795X>

Radek Janca  <https://orcid.org/0000-0003-0825-1069>

Pavel Krsek  <https://orcid.org/0000-0002-5740-3690>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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