Ultrasonographic features of focal cortical dysplasia and their relevance for epilepsy surgery

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OBJECTIVE Surgery has proven to be the best therapeutic option for drug-refractory cases of focal cortical dysplasia (FCD)-associated epilepsy. Seizure outcome primarily depends on the completeness of resection, rendering the intraoperative FCD identification and delineation particularly important. This study aims to assess the diagnostic yield of intraoperative ultrasound (IOUS) in surgery for FCD-associated drug-refractory epilepsy.

METHODS The authors prospectively enrolled 15 consecutive patients with drug-refractory epilepsy who underwent an IOUS-assisted microsurgical resection of a radiologically suspected FCD between January 2013 and July 2016. The findings of IOUS were compared with those of presurgical MRI postprocessing and the sonographic characteristics were analyzed in relation to the histopathological findings. The authors investigated the added value of IOUS in achieving completeness of resection and improving postsurgical seizure outcome.

RESULTS The neurosurgeon was able to identify the dysplastic tissue by IOUS in all cases. The visualization of FCD type I was more challenging compared to FCD II and the demarcation of its borders was less clear. Postsurgical MRI showed residual dysplasia in 2 of the 3 patients with FCD type I. In all FCD type II cases, IOUS allowed for a clear intraoperative visualization and demarcation, strongly correlating with presurgical MRI postprocessing. Postsurgical MRI confirmed complete resection in all FCD type II cases. Sonographic features correlated with the histopathological classification of dysplasia (sonographic abnormalities increase continuously in the following order: FCD IA/IB, FCD IC, FCD IIA, FCD IIB). In 1 patient with IOUS features atypical for FCD, histopathological investigation showed nonspecific gliosis.

CONCLUSIONS Morphological features of FCD, as identified by IOUS, correlate well with advanced presurgical imaging. The resolution of IOUS was superior to MRI in all FCD types. The appreciation of distinct sonographic features on IOUS allows the intraoperative differentiation between FCD and non-FCD lesions as well as the discrimination of different histological subtypes of FCD. Sonographic demarcation depends on the underlying degree of dysplasia. IOUS allows for more tailored resections by facilitating the delineation of the dysplastic tissue.

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KEYWORDS focal cortical dysplasia; malformations of cortical development; intraoperative ultrasound; intraoperative sonography; epilepsy surgery

EPILEPSY affects more than 50 million people worldwide.⁵⁴ Approximately one-third of patients show inadequate seizure control with antiepileptic drugs (AEDs).^{31,32} In children, focal cortical dysplasia (FCD) is the most frequent underlying pathology, accounting for more than 50% of cases.⁴ FCD was first described by Taylor et al. in 1971⁵⁰ and its classification has since undergone several modifications.^{37,40,49} In 2011, the first international

consensus classification was released, differentiating 3 main categories of FCD and 9 subtypes,⁵ which have been widely used ever since.³⁹ In FCD-associated epilepsy, seizure onset usually occurs in early childhood^{39,42,53} and the clinical course is often severe, with high seizure frequency, high rates of status epilepticus, and poor AED response.¹⁸ FCDs often escape detection on conventional MRI.^{9,13,27,30} However, recent technological advances, particularly

ABBREVIATIONS AED = antiepileptic drug; ECoG = electrocorticography; EEG = electroencephalography; FCD = focal cortical dysplasia; ILAE = International League Against Epilepsy; IOUS = intraoperative ultrasound.

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TABLE 1. Overview of available literature regarding the use of IOUS in patients with FCD

Authors & Year	Total Cases	FCD Type	IOUS			Sz Outcome (Engel class)
			Identification	Clear Demarcation	Features	
Miller et al., 2008	1	IIB	Yes	Yes	Clear HE	I
Miller et al., 2011	5	IA	Yes	No	Faint HE	II
		IB	No	No	None	II
		IIB*	Yes	Yes	Clear HE	I
		II	Yes	Yes	Clear HE	II
		II	Yes	Yes	Clear HE	II
Lee et al., 2014	1	IIA	Yes	Yes	Clear HE	I

HE = hyperechogenicity; Sz = seizure.

* Same case as in Miller et al., 2008.

MRI postprocessing techniques such as morphometric analysis,^{23,24,52} curvilinear reformatting,²⁵ and quantitative FLAIR analysis²⁰ increasingly allow for FCD detection and, consequently, for resection.

Surgery is the most promising intervention to achieve seizure control in FCD-associated drug-resistant epilepsy. The reported postsurgical freedom from seizures ranges widely—between 33% and 90%,^{9,10,12,15,21,22,47–49,51} depending to a great extent on presurgical candidate selection. The identification of the precise extent of the dysplastic cortical region and, consequently, its complete resection has proven to be the single most important prognostic factor for postsurgical seizure freedom.^{12,15,26,29,41,43} Seizures may originate from the center as well as the periphery of the FCD, and the regions of most severe dysplasia do not necessarily overlap with the regions of highest epileptogenicity. Thus, complete FCD resection, as opposed to a resection of the central part of the lesion or of its most dysplastic areas, is crucial for surgical success.⁶ Intraoperative tools currently used to define lesion borders include electrocorticography (ECoG), neuronavigation, and intraoperative MRI, as well as visual and tactile information. However, all of these tools have their intrinsic limitations.

Intraoperative ultrasound (IOUS) is a promising tool for intraoperative anatomical guidance, particularly regarding the demarcation of lesion borders, thereby enabling more complete resection. The efficacy of IOUS in surgery for FCD-associated drug-resistant epilepsy has been indicated by Miller et al. in a case report in 2008³⁵ and in a retrospective 5-patient series in 2011,³⁶ as well as by Lee et al. in a case report in 2014³³ (Table 1). Our study aimed to extend previous research in this field by systematically and prospectively assessing the diagnostic yield of IOUS in surgery for FCD-associated drug-resistant epilepsy in a larger cohort. For this purpose, we compared IOUS findings with those of presurgical postprocessed MRI, and we analyzed IOUS features in relation to the histologically confirmed FCD subtype. We investigated the added value of IOUS in improving completeness of resection and, thus, postsurgical seizure outcomes.

Methods

Patient Selection

We prospectively enrolled 15 consecutive patients with

drug-resistant focal epilepsy associated with a radiologically suspected FCD who underwent epilepsy surgery in our institution between January 2013 and July 2016. All patients received comprehensive presurgical evaluation according to a standard protocol in the Swiss Epilepsy Center at Klinik Lengg in Zurich, the University Hospital Zurich, and/or the University Children's Hospital Zurich and were referred for surgical treatment by an interdisciplinary case management board. All patients and/or their parents gave their written informed consent for the participation in this study. The study was approved by the local ethics committee.

Presurgical Evaluation

Demographics and Epilepsy Course

Systematically and prospectively collected data included demographics (sex, age at surgery); epilepsy history (age at epilepsy onset, duration of epilepsy to surgery, seizure classification according to the International League Against Epilepsy [ILAE] 2017¹⁹ system); seizure frequency at surgery; presurgical AED treatment; prior epilepsy surgery; presurgical neurological and neuropsychological deficits; and psychiatric comorbidities.

EEG Studies

All patients underwent long-term scalp electroencephalography (EEG), including ictal recordings. In addition, 9 patients underwent invasive EEG in a preceding, separate surgery, with subdural grid and strip electrodes and/or with stereotactically implanted depth electrodes. Invasive electrode positions were visualized in 3D format according to the postimplantation MRI.²⁸

Preoperative MRI

MRI was visually reviewed regarding the classification and extent of lesions, including the presence of a secondary pathology. In addition, MRI postprocessing techniques (morphometric analysis,²⁴ curvilinear reformatting,²⁵ and quantitative FLAIR analysis²⁰) were applied to improve FCD detection and delineation. These tools serve to highlight MRI abnormalities suspicious for FCD—such as abnormal gyral patterns, abnormally wide and/or deep sulci, increased cortical thickness, and blurring of the gray-white-matter junction, as well as abnormal cortical

TABLE 2. Demographic and clinical data according to histological result in 15 patients with FCD-associated epilepsy

Histological Type	Sex	Age at Op (yrs)	Age at Epilepsy Onset (yrs)	Duration of Epilepsy (yrs)*	Sz Classification (ILAE 2017)				Preop Sz Frequency (Szs/wk)	Preop Neurological Abnormalities		
					FO-a	FO-ia	2° TC	SE		F	NP	P
FCD IA	M	16	7	9	Yes	No	No	No	0.5	No	Yes	No
FCD IB	F	44	4	40	Yes	Yes	Yes	No	21	Yes	Yes	Yes
FCD IC	M	4	0.5	3.5	Yes	Yes	No	No	14	No	Yes	Yes
FCD IIA	M	15	7	8	Yes	Yes	No	No	0.5	No	Yes	No
FCD IIA	M	38	0.5	37.5	Yes	Yes	Yes	No	14	No	Yes	No
FCD IIA	M	1	0.5	0.5	Yes	Yes	Yes	Yes	7	No	Yes	No
FCD IIA	F	15	4	11	Yes	Yes	Yes	No	10	Yes	Yes	No
FCD IIA	F	3	0.5	2.5	No	Yes	No	No	8	No	Yes	No
FCD IIB	M	34	3	31	Yes	Yes	Yes	Yes	14	Yes	Yes	Yes
FCD IIB	M	33	8	25	No	Yes	Yes	No	21	No	Yes	No
FCD IIB	F	29	15	14	No	Yes	Yes	No	7	No	Yes	Yes
FCD IIB	F	1	0.5	0.5	Yes	No	No	No	56	No	Yes	No
FCD IIB	F	6	4.5	1.5	Yes	Yes	No	No	7	No	No	No
FCD IIB	F	7	2	5	No	Yes	Yes	No	1	No	Yes	Yes
Gliosis	M	4	0.5	3.5	Yes	Yes	No	No	70	No	Yes	No

F = focal; FO-a = focal onset, aware; FO-ia = focal onset, impaired awareness; NP = neuropsychological; P = psychiatric; SE = status epilepticus; 2° TC = focal to bilateral tonic clonic.

* Duration at time of surgery.

or subcortical signal intensity, including the transmantle sign. These criteria were based on current literature regarding MRI features of FCDs.^{2,9,13,25,30}

Surgery and Intraoperative Guidance

Neuronavigation (Stealth Station; Medtronic) was used in all cases. For this purpose, the localization of the lesion, as indicated by postprocessed MRI, was transferred as a bright marker into a 3D T1-weighted image, which in turn was loaded into the neuronavigation system. After craniotomy and dura mater opening, IOUS was applied, allowing for anatomical orientation, morphological comparison to preoperative imaging, and delineation of the lesion. For this high-resolution intraoperative imaging we used an iU22 Ultrasound System with a real-time L15–7 intraoperative probe (7–15 MHz extended frequency with a phased linear array of 128 elements including a 23-mm effective aperture length, probe tip measure 11 × 31 mm; Philips).⁸ Intraoperative ECoG was performed in all cases. Thus, the final extent of resection finding was based on the postprocessed preoperative MRI, IOUS, and intraoperative ECoG.

Histopathological Evaluation

Resection specimens were analyzed by the Department of Neuropathology, University Hospital Zurich. To increase diagnostic certainty, an additional histopathological evaluation was performed in the European FCD Reference Center in Erlangen. FCDs were categorized according to the ILAE classification system.³

Follow-Up

Clinical and EEG follow-up was scheduled at 3, 6, and 12 months after surgery and then yearly in cases of sei-

zure control or at appropriate intervals in cases of seizure recurrence. MRI was performed 3 months after surgery to assess for potential residual dysplasia, including postprocessing evaluations as well as coregistration with presurgical MRI. Epilepsy course, AED tapering, and neurological deficit were noted. The classification of postsurgical seizure outcome was performed according to the Engel classification system.¹⁶

Data Analysis

Due to the small sample size, statistical analysis is provided in a descriptive manner.

Results

Demographics and Epilepsy Course

Seven female (47%) and 8 male (53%) patients were included in our study. The demographic data and the presurgical epilepsy course are given in Table 2. Epilepsy onset occurred at a mean of 3.5 years (SD 4.1, range 0.5–15 years), the mean duration from epilepsy to surgery was 12.4 years (SD 13.4, range 0.5–40 years), and the mean age at surgery was 16.7 years (SD 14.5, range 1–44 years). All but 3 patients were experiencing daily seizures at the time of surgery despite multiple AED trials. None of the patients had previously undergone epilepsy surgery. All but one of our patients presented with focal neurological deficit, neuropsychological impairment, or psychiatric comorbidities prior to surgery.

Presurgical Evaluation

Topographical and morphological features of the suspected dysplastic areas are presented for all patients in Table 3 and for illustrative cases in Figs. 1–3. Blurring of the

TABLE 3. Imaging features and outcome according to histological result in 15 patients with FCD-associated epilepsy

Histological Type	Topography			MRI Morphology				IOUS Morphology			Clear Margins on IOUS	Residual EDs on iCoG	Postop Residual FCD	Sz Outcome* (Engel class)
	Side	Lobe	Gyr/Sulci	gwmj-b	ICT	A-G/S	T2-c	T2-sc	TMS	HE-c	HE-gwmj	HE-sc	ICT	
FCD IA	Rt	Parietal	IPS	Yes	No	No	No	No	No	+	+	-	-	No
FCD IB	Rt	Parietal	CS/post-CS	Yes	No	No	No	No	No	+	+	-	-	No
FCD IC	Rt	Temporal	TP/amyg/HH	Yes	Yes	No	No	Yes	No	++	+	+	-	Yes
FCD IIA	Lt	Frontal	SFS/F1	Yes	Yes	Yes	Yes	Yes	Yes	++	++	++	++	No
FCD IIA	Lt	Parietal	Post-CS	Yes	Yes	Yes	Yes	Yes	Yes	++	++	+	+	No
FCD IIA	Rt	Frontal	F1	Yes	Yes	Yes	Yes	Yes	Yes	++	+++	++	++	No
FCD IIA	Lt	Frontal	Pre-CS	Yes	Yes	Yes	Yes	Yes	Yes	++	++	++	+	Yes
FCD IIA	Rt	Temporal	TP	Yes	Yes	Yes	Yes	Yes	No	++	++	+	++	Yes
FCD IIB	Rt	Frontal	F1 (mS)	Yes	Yes	Yes	Yes	Yes	Yes	+++	+++	++	++	No
FCD IIB	Rt	Frontal	Pre-CS	Yes	Yes	Yes	Yes	No	No	+++	+++	+++	+++	No
FCD IIB	Lt	Temporal	ITS/T3	Yes	Yes	Yes	Yes	Yes	Yes	+++	++	+++	+++	Yes
FCD IIB	Lt	Frontal	IFS	Yes	Yes	Yes	Yes	Yes	No	++	+++	++	++	No
FCD IIB	Lt	Frontal	F1 (mS)	Yes	Yes	Yes	Yes	Yes	Yes	+++	+++	+++	++	No
FCD IIB	Lt	Frontal	F1 (mS)	Yes	Yes	Yes	Yes	Yes	No	+++	+++	+++	+++	No
Glosis	Lt	Temporal	TP/Fu/LTOS	Yes	No	No	Yes	Yes	No	-	-	+	-	No

A-G/S = atypical gyration/sulcation; amyg = amygdala; CS = central sulcus; EDs = epileptiform discharges; Fu = fusiform (lateral temporo-occipital gyrus); F1 = superior frontal gyrus; gwmj-b = gray-white-matter junction blurring; HE-c = cortical HE; HE-gwmj = HE at the gray-white-matter junction; HE-sc = subcortical HE; HH = head of hippocampus; ICT = increased cortical thickness; iCoG = intraoperative ECOG; IFS = inferior frontal sulcus; IPS = intraparietal sulcus; ITS = inferior temporal sulcus; LTOS = lateral temporo-occipital sulcus; mS = medial sulcus; NA = not applicable; SFS = superior frontal sulcus; TMS = transmantle sign; TP = temporal pole; T2-c = cortical T2 hyperintensity; T2-sc = subcortical T2 hyperintensity; T3 = inferior temporal gyrus; -, +, ++, +++ = degree of HE.

* At last follow-up.

† Questionable residual FCD.

FIG. 1. Examples of pre-, intra-, and postoperative imaging in a patient with type IA FCD in the depth of the right intraparietal sulcus. Preoperative MRI with postprocessing (example sequence shown) allowed us to identify an area of subtle blurring of the gray-white-matter junction suspicious for the presence of FCD. Despite very discrete signal alterations on preoperative MRI, IOUS allowed us to depict the dysplastic area with high resolution by showing hyperechogenicity in the cortex and the underlying gray-white-matter junction. Topographical and morphological features correlated well to preoperative imaging. However, a sharp demarcation of the altered area was not possible, resulting in subtotal resection, with residual dysplasia seen with coregistration between pre- and postoperative MRI.

gray-white-matter junction was the most consistent feature pointing to FCD in our cohort. Radiologically, dual pathology was found in a single patient, who presented with left hippocampal sclerosis in addition to a suspected left mesiotemporal FCD. It should be noted, however, that histopathological investigation did not confirm FCD, only showing nonspecific gliosis in this case.

Intraoperative Ultrasound

IOUS showed signal abnormalities in the region of suspected FCD in all cases. These sonographic abnormalities presented a high anatomical correlation with the features suspicious for FCD on preoperative MRI (Figs. 1–3), whereas IOUS resolution was superior to MRI in all cases. In addition, the sonographic features of the lesions correlated well with histopathological findings (Fig. 4). In all but one patient, IOUS showed specific and circumscribed signal abnormalities: histopathological investigation confirmed FCD. In a single patient, IOUS showed diffuse signal alterations with a blurry cortical and subcortical hyperechogenicity: histopathological studies revealed only nonspecific gliosis.

In cases with specific and circumscribed signal abnormalities corresponding to histologically verified FCD, the degree of cortical and subcortical signal alterations correlated to the underlying degree of dysplasia; i.e., to the FCD subtype. In the 3 cases of FCD type I, the dysplastic

cortical areas showed discrete hyperechogenicity with a blurred border toward the underlying white matter, albeit without any white matter changes. In FCD type I, the dysplastic area was thus identifiable, but the precise demarcation of its borders was challenging. FCD types IA and IB presented with almost identical features in IOUS, whereas FCD type IC was characterized by a higher degree of cortical hyperechogenicity. FCD type II presented with more pronounced sonographic abnormalities, including marked cortical hyperechogenicity, increased cortical thickness, blurred and hyperechogenic gray-white-matter junction, and variably increased white matter signal. These changes were more prominent in FCD type IIB. In FCD type II, the dysplastic area was not only identifiable, but the precise demarcation of its borders was facilitated by these pronounced signal changes. IOUS findings are given in Table 3.

Intraoperative Electrocorticography

Intraoperative ECoG following the sonographically guided resection revealed residual epileptic discharges in only 2 cases (Table 3). In one of these patients, further ECoG-guided resection was limited by the localization of the epileptic discharges within the primary motor area. In the second case the residual epileptic activity in ECoG led to an extension of the previous resection; in repeat ECoG, no unequivocal epileptic discharges were noted.

FIG. 2. Examples of pre-, intra-, and postoperative imaging in a patient with type IIA FCD in the depth of the superior precentral sulcus. Preoperative MRI with postprocessing (example sequence shown) revealed subtle cortical and subcortical T2-weighted and FLAIR hyperintensity, discrete increase in cortical thickness, and blurring of the gray-white-matter junction. On IOUS, this area suspicious for FCD could be easily identified by the marked hyperechogenicity of a thickened cortex, hyperechogenic, blurred gray-white-matter junction, and increased signal of the adjacent subcortical white matter, with high topographical-morphological correlation to preoperative imaging. Sharp demarcation of FCD borders by IOUS allowed us to perform complete resection without residual dysplasia on coregistration between pre- and postoperative MRI.

Intraoperative and Immediate Postoperative Course

The mean duration of the surgical procedure was 226 minutes (SD 54.5 minutes, median 210 minutes, range 165–355 minutes). No surgical complications such as intra- or postoperative hematoma, stroke, or wound infection were noted. Fourteen patients had an uneventful postoperative course, whereas 1 patient suffered from mild postoperative paresis and hyposensitivity in the left lower extremity after removal of a right postcentral FCD adjacent to the central sulcus. This neurological deficit was considerably improved at last follow-up.

Follow-Up

At last follow-up (between 18 and 60 months—mean 35.9, SD 11.3, median 35 months), 10 of 15 (67%) patients were completely seizure free (Engel IA) (Table 3), 1 had only simple partial nondisabling seizures, and 3 more had rare disabling seizures (Engel II). The patient with non-specific gliosis showed no worthwhile improvement (Engel IVB).

Seizure outcome varied considerably between different FCD types. Two of the 3 patients with FCD type I were completely seizure free after surgery (Engel IA), whereas the other one had only simple partial nondisabling seizures after surgery (Engel IB). Residual dysplastic cortex at the resection border was identified in the 2 patients with FCD type I (1 with FCD type IA, 1 with FCD type IB) who

achieved seizure freedom. Eight of the 11 patients with FCD type II were completely seizure free after surgery (Engel IA), and the other 3 had rare disabling seizures (Engel II). No residual dysplastic cortex was identified in any of the patients with FCD type II.

Discussion

To the best of our knowledge, this is the largest case series of IOUS utilization in epilepsy surgery, particularly in the context of FCD-associated drug-resistant epilepsy. The size of our cohort enables us to draw some reliable conclusions regarding the feasibility and added value of IOUS application in the resection of FCD.

FCD is one of the main underlying substrates in drug-resistant partial epilepsy, especially in children.⁵ Resection is the most promising therapeutic option, with incomplete resection of the dysplastic cortex posing a major risk for seizure recurrence.^{12,17,26,29} Therefore, the optimal pre- and intraoperative definition of the lesion border and its resection are the key for surgical success. Dedicated MRI sequences, including MRI postprocessing techniques, markedly improved preoperative detection. However, intraoperative tools to guide FCD resection are limited. Direct visual and tactile information is generally poor in the case of FCD compared to other lesions such as brain tumors.^{33,35} Furthermore, neuronavigation accuracy is limited by its low overall resolution and by the risk of brain shift.^{1,11,14,33,35}

FIG. 3. Examples of pre-, intra-, and postoperative imaging in a patient with type IIB FCD of the superior frontal gyrus in the region of the medial sulcus. Preoperative MRI with postprocessing (example sequence shown) revealed cortical and subcortical T2-weighted and FLAIR hyperintensity, marked increase in cortical thickness, and pronounced blurring of the gray-white-matter junction. With high topographical-morphological correlation to preoperative imaging, IOUS revealed an area of heavily increased cortical thickness and marked hyperechogenicity in the cortex, at both the gray-white-matter junction and subcortically. Lesion borders could be clearly identified. Coregistration between pre- and postoperative MRI showed no residual dysplasia.

Intraoperative MRI has been reported to be useful,^{7,46} but its application is restricted by the limited availability, high costs, associated delay of surgery, low resolution,³⁸ and absence of postprocessing techniques. Even though ECoG is of high value during FCD resection, it gives only 2D functional—and not anatomical—information, with a variable relation to the dysplastic region.³⁴ IOUS, on the contrary, is widely available and inexpensive. It has the advantage of being safe as well as quickly and repetitively applicable. IOUS interrupts the surgical procedure for only some seconds, in comparison to other intraoperative techniques such as acquisition of intraoperative MRI. It delivers real-time information, independent of brain shift, and provides 3D lesion visualization. Despite the many advantages of IOUS, only 3 studies, each reporting 1–5 cases,^{33,35,36} have addressed the use of IOUS for FCD delineation in epilepsy surgery (Table 1).

Our study confirms the added value of IOUS for FCD detection, identification, and delineation. Sonographic visualization showed high correlation with preoperative MRI, including advanced postprocessing techniques. IOUS resolution was superior to MRI in all cases. Furthermore, sonographic features were shown to correlate to the underlying histopathological findings. First, this allows for a differentiation between FCD and non-FCD lesions (e.g., gliosis, characterized by diffuse nonorganized hyperechogenicity), which may have a direct impact on surgical strategy (e.g., intended extent or completeness of resection). Second, IOUS allows surgeons to estimate the underlying FCD type, due to the strong correlation between the se-

verity of signal abnormalities and the degree of dysplasia (sonographic abnormalities increase continuously in the following order: FCD IA/IB, FCD IC, FCD IIA, FCD IIB). FCD type I, histologically defined by isolated dyslamination, showed only discrete cortical hyperechogenicity and blurring of the gray-white-matter junction. These features were similar in FCD type IA and IB, whereas they were more pronounced in the case of FCD type IC. This is in line with the histological properties of FCD types IA and IB, which are characterized by isolated radial or tangential dyslamination, whereas type IC combines these characteristics. Type II FCDs, histologically defined by the additional presence of dysmorphic neurons within the dysplastic area, showed more extensive sonographic abnormalities than with FCD I. The cortex appeared thickened and more hyperechogenic, the blurring of the gray-white-matter junction was more obvious, and there was some degree of subcortical hyperechogenicity. FCD IIB lesions (i.e., those containing balloon cells) displayed these features in an even more pronounced manner than type IIA. The clear sonographic visualization of FCD type II allowed for sharp demarcation of lesion borders in every case. Our results are in line with the reports from Miller and colleagues^{35,36} and Lee et al.³³ Miller et al. described 3 cases of FCD type IIB characterized by marked hyperechogenicity and 1 of FCD type IA with faint hyperechogenicity. In contrast to our results, sonographic visualization was not possible in an FCD type IB in this study.³⁶ The case of FCD IIA reported by Lee et al. was sonographically characterized by homogeneous hyperechogenicity.

FIG. 4. Examples showing sonographic morphology of the different FCD subtypes versus nonspecific gliosis.

In our study, the extent of resection correlated with the demarcation of lesion margins on IOUS, which again matched the degree of dysplasia. IOUS allowed for complete resection in all FCD type II cases, whereas there was some marginal residual dysplasia in 2 cases (FCD IA and IB). Reported postsurgical seizure freedom rates in patients with FCD range from 33% to 90%.^{9,10,12,15,21,22,47–49,51} The size and heterogeneity of our cohort does not allow for definitive statements regarding seizure outcome. However, the 71% Engel IA outcome is particularly favorable. Surgery in FCD type II has previously been associated with superior seizure outcome as compared to FCD type I,^{4,44,45} highlighting the challenges in the surgical approach for FCD type I. The inferior postsurgical outcome in patients with FCD type I—without IOUS—may be explained by the more difficult visualization with MRI, because cortical cellular density is only minimally altered in these FCD

types.³⁹ Patients with FCD type I in our series, however, had a favorable seizure outcome, despite the residual dysplasia. One possible explanation is that IOUS, by its high resolution, allows the surgeon to visualize and resect the regions of biologically relevant dysplasia in FCD type I, balancing the outcome between the different FCD subtypes.

This study shows the high potential of IOUS as a readily available neurosurgical tool in surgery for FCD-associated drug-resistant epilepsy, due to the excellent morphological resolution and close relation of the sonographic features to the histological degree of dysplasia. However, our findings should be interpreted with care, considering the following limitations. First, despite the reported higher resolution of IOUS, the role of MRI—and especially of postprocessing techniques—remains important and MRI cannot be replaced by IOUS. MRI is still the modality guiding

the presurgical evaluation by identifying the potential epileptogenic lesion and determining the extent of resection. Second, IOUS interpretation remains subjective, and is highly dependent on the judgment and the experience of the investigator as well as on the apparatus and its settings. Third, the histopathological limitations of the 2011 classification³ should be mentioned: the differentiation of FCD I subtypes is increasingly considered arbitrary;³⁹ they reportedly lack a clinical, imaging, or molecular phenotype. Despite the fact that the detected discrete sonographic differences between type IA/IB and IC represent such an imaging phenotype, the relevance of this differentiation remains unclear. The subdivision of FCD II into IIA and IIB has also been questioned.³⁹ Sonographically, we identified these subtypes as different entities; however, the main distinction clearly remains between types I and II. Finally, limitations are posed by the small size of our cohort, which includes many different histological subtypes, precluding statistical analysis. Further research in larger cohorts and a prospective randomized design will be needed to make clear statements regarding the prognostic value of IOUS and its effect on residual dysplasia and seizure outcome.

Conclusions

This is the largest study to date investigating the yield of IOUS in surgery for FCD-associated drug-resistant epilepsy. Morphological features identified by IOUS show a high correlation with advanced preoperative imaging and may provide a superior resolution in some cases. The distinct sonographic features allow for the intraoperative distinction between FCD and non-FCD lesions as well as between the different histological subtypes of FCD. The sharpness of sonographic demarcation depends on the underlying degree of dysplasia. IOUS facilitates the completeness of resection by clearly delineating the dysplastic area.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Akeret, Krayenbühl. Acquisition of data: Akeret. Analysis and interpretation of data: Akeret, Bellut. Drafting the article: Akeret. Critically revising the article: Bellut, Huppertz, Ramantani, König, Serra, Regli, Krayenbühl. Reviewed submitted version of manuscript: Bellut, Ramantani, Krayenbühl. Statistical analysis: Akeret. Administrative/technical/material support: Akeret. Study supervision: Krayenbühl.

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