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Intraoperative ultrasonography (ioUS) characteristics of focal cortical dysplasia (FCD) type II b

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ABSTRACT

Purpose: Focal cortical dysplasia (FCD) is one of the major causes of drug-resistant epilepsy. Surgery has proved to be the treatment of choice, however up to a third of patients experience only partial resection. Ill-defined borders and lesions embedded in eloquent areas are two of the main drawbacks of FCD surgery. Preliminary experiences with intraoperative ultrasound (ioUS) have proved its feasibility and potential. We analyzed FCD' ioUS findings in our patients with FCD and compared them with magnetic resonance (MRI) ones.
Methods: We retrospectively reviewed all records of patients with focal medically refractory epilepsy who underwent ioUS guided surgery between November 2014 and October 2017. Lesions other than FCD or FCD associated with other pathological entities were not considered. Patients' preoperative MRI and ioUS features were analyzed according to up-to-date literature and than compared.
Results: A homogeneous population of five patients with type IIb FCD was evaluated. Focal cortical thickening and cortical ribbon hyper-intensity, blurring of the grey-white matter junction and hyper-intensity of the subcortical white matter on T2-weighted/FLAIR images were present in all patients. Cortical features had a complete concordance between ioUS and MRI. In particular ioUS thickening and hyper-echogenicity of cortical ribbon were identified in all cases (100%). Contrary, hyper-echoic subcortical white matter was detected in 60% of the patients. IoUS images resulted in clearer lesion borders than MRI images.
Conclusion: Our study confirms the potentials of ioUS as a valuable diagnostic tool to guide FCD surgeries.

1. Introduction

Worldwide, 50 to 60 million people suffer from epilepsy and up to one third can develop drug-resistance [1]. Focal cortical dysplasia (FCD) is a wide group of heterogeneous pathological entities affecting various aspects of the brain, such as cortex architecture, grey- white matter junction and subcortical white matter composition [2]. The International League Against Epilepsy (ILAE) has recently proposed a three-tiered classification system of clinical-pathological subtypes. Type I is characterized by aberrant radial (Ia) or tangential (Ib) lamination of the neocortex or a combination of the two (Ic). Type IIa is typified by cortical laminar disruption with dysmorphic neurons and without balloon cells. On the contrary, in type IIb, both dysmorphic neurons and balloon cells are present. Type III is represented by an FCD associated with other epileptogenic lesions acquired in early life [3]. FCD is responsible for up to 50% of intractable epilepsies, usually affecting younger patients, compared to drug-resistant seizures due to other aetiologies (ex. tumours, hippocampal sclerosis) [4]. Complete surgical removal of the dysplastic area leads to post-surgical seizure control in up to 80% of patients. Despite this method being the treatment of

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choice, in about one third of patients, surgery is limited to a partial resection [4]. Inexact intraoperative FCD extension estimation or lesions embedded in eloquent brain areas lead to incomplete resections [4–6]. Pre-surgical planning is not standardized and is based on clinical and imaging exams. A standard epileptic non-invasive presurgical evaluation (comprising a high-resolution magnetic resonance imaging (MRI)) usually suffices to determine whether a patient is a candidate for a resection procedure. Although MRI features in FCD are well established [7] especially in more advanced dysplastic lesions, the overall sensitivity is only 77%. Inter-ictal fluorodeoxyglucose positron emission tomography (FDG-PET) and subtraction ictal single photon emission computed tomography (SPECT) co-registration to MRI images increased sensitivity up to 87% and 95%, respectively [8].

Intraoperative ultrasound (ioUS) is a widely available, inexpensive, real-time tool allowing the visualization of both intra- and extra-axial brain tumours [9–12] and medullary and vascular lesions [13,14]. In addition, ioUS is able to depict structures adjacent to the resection site, such as blood vessels. It guarantees post-surgical cavity exploration as well.

In literature there is a paucity of studies evaluating the role of ioUS in FCD patients before surgery [15–18]; ioUS has been employed mostly for its ability to localize FCD, but a thorough description of its US features is lacking. The aims of the present study are to illustrate the ioUS imaging characteristics in type IIb FCD and also to compare them with preoperative MRI features, in order to facilitate surgical planning and intra-operative image guidance.

2. Materials and methods

2.1. Patient population

Our Institutional Review Board approved the use of intra-operative US as a part of standard neurosurgical procedures. This study was based on routinely collected, anonymized data with a waiver of informed consent. We retrospectively evaluated all patients with focal medically refractory epilepsy who underwent ioUS guided surgery between November 2014 and October 2017. Patients with tumours, vascular lesions, sequelae of trauma and malformations of cortical development other than FCD were not considered in our study. The ioUS examination was performed by two neurosurgeons with experience in epilepsy surgery and ioUS (GT, FP). Surgical specimens were analyzed by an experienced pathologist who defined the exact FCD type according to ILAE classification [3]. All specimens were confirmed as being type IIb FCD.

2.2. Pre-surgical diagnostics imaging

All patients underwent an MRI scan on a 1.5-Tesla MRI scanner (Siemens Avanto, Erlangen, Germany) according to our institute's standard protocol. Our protocol is based on the following para-coronal sequences oriented on temporal lobes, added to the morphological T1 and T2-weighted sequences: para-coronal turbo spin-echo (SE) fluid-attenuated inversion-recovery (FLAIR) T2-weighted sequence (8330/96/2500/2 [TR/TE/TI/excitations], 256 × 256 matrix, 240-mm field of view, 3 mm slice thickness, 10% intersection gap, turbo factor of 11); para-coronal turbo SE T2-weighted sequence (4230/123/3 [TR/TE/excitations], 512 × 512 matrix, 230-mm field of view, 3-mm section thickness, 0% intersection gap, turbo factor of 21); and para-coronal turbo SE inversion- recovery (IR) T1-weighted sequence (5650/71/400/2 [TR/TE/TI/excitations], 512 × 512 matrix, 230-mm field of view, 3-mm section thickness, 20% intersection gap, turbo factor of 15). In all patients, 3D volume fast field echo T2-weighted images were also acquired in the transverse plane (3000/457/1 [TR/TE/excitations], 80° flip angle, 512 × 512 matrix, 250-mm field of view, 1.04-mm-thick contiguous sections); the source images were subsequently reconstructed in sagittal and coronal sections.

MR images were analyzed by two neuroradiologists (AGG, LDI) in consensus, both of which who had more than twenty years of experience. The following image features were considered: focal cortical thickening; blurring of the junction between grey and white matter; hyper-intensity on T2-weighted/FLAIR images of grey matter and of subcortical white matter; trans-mantle sign (hyper-intensity on T2-weighted/FLAIR images extending from the cortex to the ventricle); hypo-intensity in the subcortical white matter on heavily T1-weighted images; and focal brain hypoplasia. PET scan, 3.0 T MRI, diffusion tensor imaging (DTI) and functional MRI (fMRI) were performed if clinically requested.

2.3. Intraoperative imaging and resection

In all patients neuronavigation, based on preoperative MRI, coupled with intraoperative electrocorticography (EcoG) was performed to localize the lesion site. After the bone flap was removed, and haemostasis reached, the ioUS probe was wrapped in a surgical sterile transparent plastic sheath (Civco, USA) and coupled with sterile ultrasonic compatible gel. Before transdural insonation the surgical field was irrigated with sterile saline solution to eliminate the presence of air or blood clots between the dura and the transducer. IoUS evaluation was performed using a last generation US device (MyLab Twice, Esaote, Italy) equipped with both a linear multifrequency (3–11 MHz) probe and a high frequency (10–22 MHz) probe. Probe selection was tailored according to lesion localization in the preoperative MRI. Scan and focus depth, focus dimension and gain compensation were adjusted before FCD analysis. The lesion, previously identified on MRI images, was evaluated on both axes until a comprehensive definition of its boundaries was reached. A tailored lesionectomy was planned according to preoperative MRI, EcoG and real-time ioUS. Surgical specimens were sent to neuropathology for histological evaluation. EcoG (by means of a 20 contact grid associated with eloquent motor cortex monitoring by neurophysiological stimulation) was repeated after the excision to verify the absence of ictal activity. The whole intra-operative procedure used to perform ioUS imaging has been extensively described in a previous paper from our group [19].

IoUS images were reviewed in consensus by two observers (FP, AGG) with more than 5 years of experience in US. Relying on the few ioUS findings available in previous reports, the following US imaging features were considered [15–18]: focal cortical thickening; blurring of the junction between grey and white matter; grey matter hyper-echogenicity; and subcortical white matter hyper-echogenicity. The ability of ioUS to create imaging of the trans-mantle sign and focal brain hypoplasia was also analyzed and compared to preoperative MRI results.

3. Results

3.1. Patients' characteristics at preoperative evaluation

Five patients (3 males, 2 females; mean age at surgery 27 years old, 5–52) all with type IIb FCD were evaluated. In all patients the combination of preoperative inter-ictal EEG, long term video-scalp EEG monitoring and MRI demonstrated findings compatible with FCD located in the right frontal lobe.

3.2. Pre-surgical MRI findings

At the MRI evaluation, all patients (100%, 5/5) had focal cortical thickening and hyper-intensity of the cortical ribbon, blurring of the grey-white matter junction and hyper-intensity of the subcortical white matter on T2-weighted/FLAIR images. Other common signs were the trans-mantle sign and the hypo-intensity of white matter on T1-IR images which were present in 80% (4/5) and 60% (3/5) of the patients, respectively. Only one patient had absence of both the trans-mantle sign and the hypo-intensity of the white matter on T1-IR images. None

Table 1
A summary of preoperative MRI (symbols on the right) and ioUS (symbols on the left) findings in each patient. Positive and negative findings are represented with (+) and (–), respectively.

MRI findings	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	ioUS findings
Focal cortical thickening	+/+	+/+	+/+	+/+	+/+	Focal cortical thickening
Blurring of GW matter junction	+/–	+/+	+/–	+/–	+/–	Blurring of GW matter junction
T2 hyperintense grey matter	+/+	+/+	+/+	+/+	+/+	Hyperechoic grey matter
T2 hyperintense white matter	+/–	+/–	+/+	+/+	+/+	Hyperechoic white matter
T1 hypintense white matter	–	+	+	–	+	
Transmantle sign	+/–	+/–	+/+	–/–	+/–	Transmantle sign
Focal brain hypoplasia	–/–	–/–	–/–	–/–	–/–	Focal brain hypoplasia

had focal brain hypoplasia. In three patients (60%, 3/5) MRI abnormalities involved a single lobule or sulcus: one (20%, 1/5) where FCD involved at least two lobules and the sulcus in between and in another one (20%, 1/5) where the alterations involved the entire right frontal lobe. No other concomitant findings were seen at the MRI evaluation. Three patients underwent PET imaging which showed areas of hypometabolism in the right frontal lobe. An additional 3 T MRI, with a similar scanning protocol to the 1.5 T MRI, was performed in two patients. The exam led to a better definition of lesion relations with eloquent areas thanks to fMRI and DTI but did not provide additional information compared to 1.5 T MRI images. A detailed list of pre-surgical MRI findings is reported in Table 1.

3.3. IoUS evaluation, its findings and lesions' characteristics

High frequency (10–22 MHz) or low frequency (3–11 MHz) probes were used for image acquisition in 3 patients and 1 patient, respectively; one patient was scanned with both probes (Fig. 1). IoUS confirmed the localization of the lesions previously identified by MRI in all cases (100%, 5/5) allowing a thorough comprehension of the surgical field architecture before opening the dura mater with detection of adjacent vascular structures and related anatomical landmarks (ex. cerebral falx, basal ganglia, lateral ventricule) in all cases (100%, 5/5). Compared to the normal ioUS appearance of the cerebral cortex (hypoechoic), a thickened hyper-echoic cortical ribbon was present in all cases (100%, 5/5) and a higher echogenicity of the subcortical white matter in 60% of the patients (3/5). Only one patient had a blurred grey-white matter junction (20%, 1/5) and none of them had evidence of focal brain atrophy. The thickening of the cortical layer determined a slightly hypertrophic appearance of the dysplastic area in all cases (100%, 5/5). The trans-mantle sign was detected in only one patient (20%, 1/5) (Fig. 1).

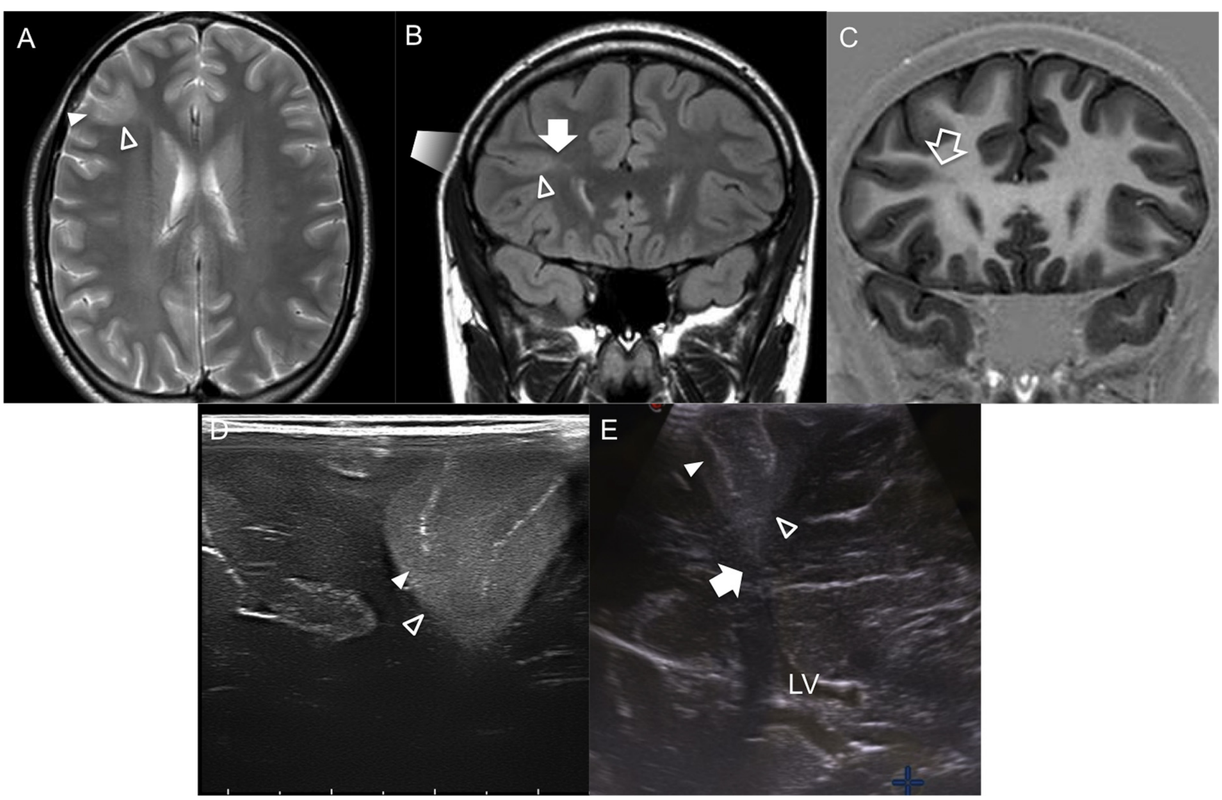

Fig. 1. Differences between high and low frequency probe findings.
Axial T2 (A) and para-coronal FLAIR weighted images (B, orthogonal to A) highlight the presence of a thick hyper-intense cortical ribbon (arrowhead) surrounded by a hyper-intense white matter (empty arrowhead). The grey-white matter junction and lesion boundaries appear blurred. Trans-mantle sign (arrow in B) and a wedge-shaped white matter hypo-intensity (empty arrow in C) are identified on FLAIR and T1-PSIR image (C, acquired orthogonal to A), respectively. High-frequency para-coronal ioUS image (D, probe orientation is shown in B, with a faded white trapezoid; probe was also slightly tilted in posterior direction) shows the concomitance of thickened, hyper-echoic, grey matter (arrowhead) and hyper-echoic white matter (empty arrowhead). The junction between the two structures is visible and FCD's boundaries are well demarcated. A low-frequency probe image on para-coronal plane (E, angled similarly to D) demonstrates the trans-mantle sign (arrow) reaching the border of the lateral ventricle (LV).

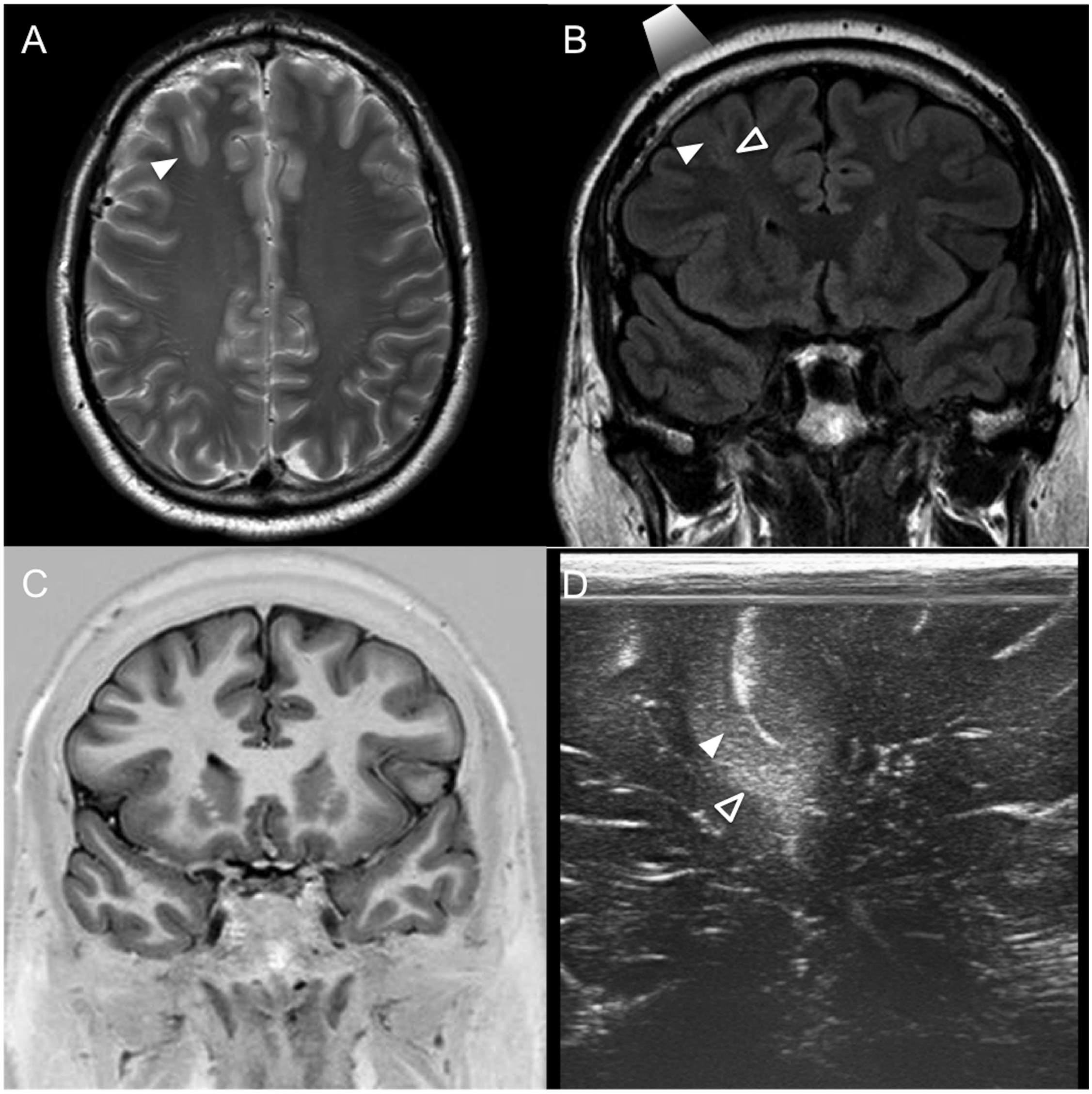

Fig. 2. MRI and ioUS findings in a 26 years old male.
Axial T2 (A) and para-coronal FLAIR weighted images (B, orthogonal to A) show a thick hyper-intense cortical ribbon (arrowhead) surrounded by a hyper-intense white matter (empty arrowhead in B). White matter hypo-intensity is absent on T1-PSIR image (C, orthogonal to A). High spatial resolution high-frequency probe para-coronal ioUS image (D, probe orientation is shown in B, with a faded white trapezoid) demonstrates thickened, hyper-echoic grey matter (arrowhead), the surrounding hyper-echoic white matter (empty arrowhead) and the well demarcated junction between the two structures.

3.4. Comparison between MRI and ioUS findings

A complete agreement between preoperative MRI and ioUS was found only on cortex features. The cortical layer appeared thickened and hyper-intense on T2/FLAIR weighted images and as thickened, hyper-echoic, grey matter on ioUS (Figs. 1–3). The blurring of the grey-white matter junction with MRI had a low rate (20%, 1/5) of ioUS counterparts. Also hyper-intensity of the subcortical white matter on T2-weighted/FLAIR images had equivalent white matter hyper-echogenicity in only 3/5 (60%) of patients (Fig. 3). The agreement between MRI and ioUS findings is detailed in Table 1. Perfect agreement between MRI and ioUS features was not present in any (0%, 0/5) of the five patients.

3.5. Surgical technique and outcome

All lesionectomies were uneventful. In 3 patients resection was extended further than the preoperative MRI FCD's boundaries until a significant electrographic quiescence was recorded. In all these patients ioUS better delimited lesional boundaries compared to MRI. Postoperative MRI evaluation showed, in all patients, complete resection of the FCD (Fig. 4). At 2 years follow-up, one out of 5 patients is in Engel Class IB, while the others are in IA.

4. Discussion

Our study described, although in a relatively small pool of patients, the B-mode ioUS patterns and characteristics of FCD type IIb. We also demonstrated that B-mode has a very high concordance rate with preoperative MRI findings, showing the potentials of ioUS as a real-time image guidance tool for surgical removal. Unfortunately, the small number of patients included in this study does not allow for any statistical evaluation.

4.1. IoUS FCD features

On B-Mode images, a healthy cortical ribbon is usually thin and homogenously hypo-echoic, and therefore, easily differentiated from

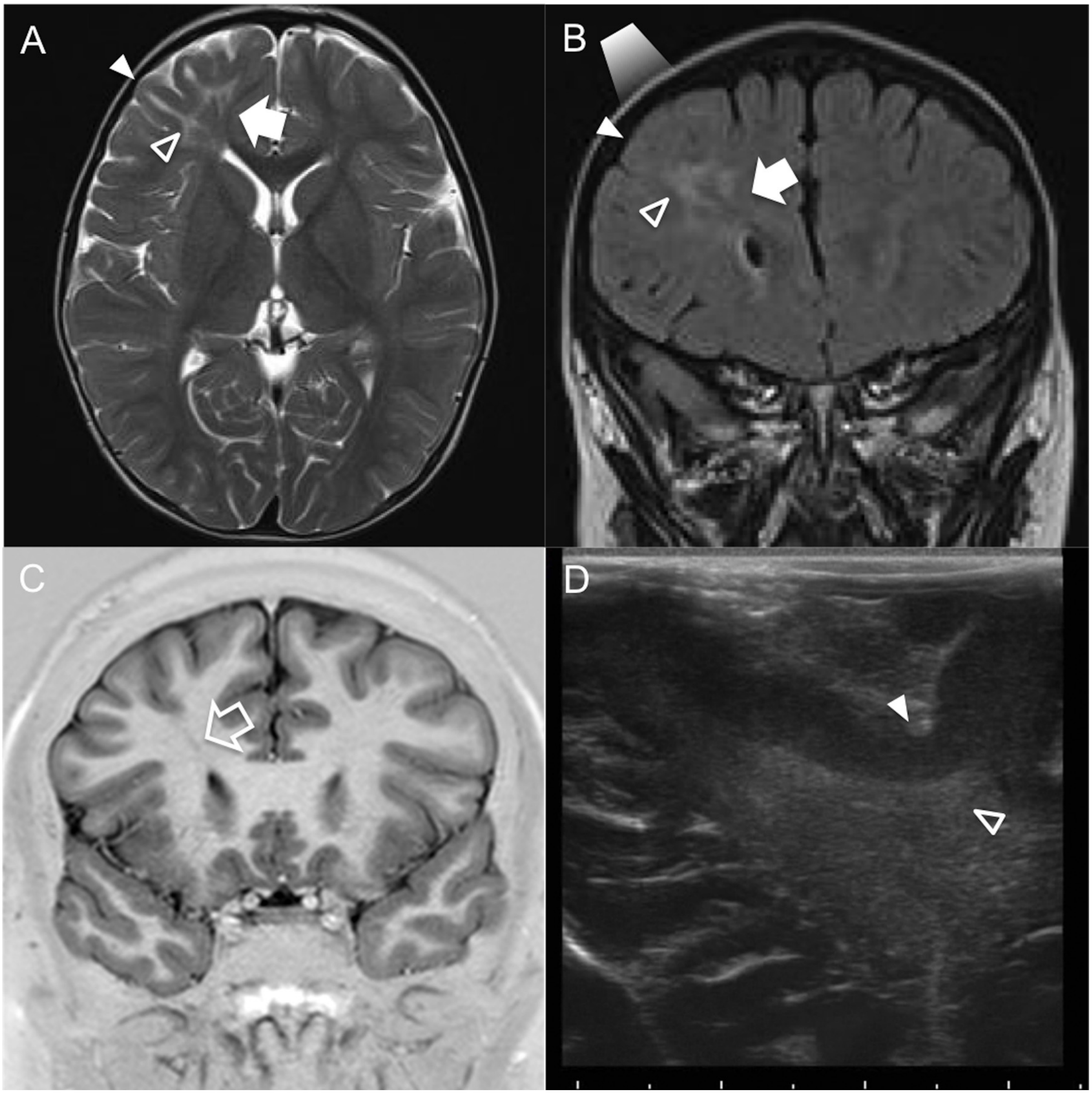

Fig. 3. MRI and ioUS findings in a 52 years old male.
Both axial T2 (A) and para-coronal FLAIR weighted images (B, orthogonal to A) show a diffuse cortical thickening (arrowhead), a white matter hyper-intensity (empty arrowhead) and trans-mantle sign (arrow). A thin longitudinal white matter hypo-intensity is present on T1-PSIR weighted image (C, orthogonal to A). The corresponding high-frequency probe paracoronal ioUS image (D, probe orientation is shown in B, with a faded white trapezoid) depicts a thickened, hyper-echoic cortical ribbon (arrowhead) compared to the mesial sulci. A hyper-echoic white matter (empty arrowhead) and the junction between the two structures are also visible.

the hyper-echoic subcortical white matter. All the dysplastic lesions demonstrated a thickened, hyper-echoic, cortical layer in comparison to the adjacent normal gyri. The evaluation of subcortical white matter anomalies is not particularly challenging since they appear brighter compared to the adjacent hyper-echoic white matter. This white matter hyper-echogenicity is likely related to the reduction of myelin staining seen at histochemical evaluation in routine neuropathological analysis of surgical specimens [3]. Both these ioUS findings had high concordance rates with T2- weighted/FLAIR images. The high frequency probe stressed the distinction between healthy and dysplastic white matter providing better anatomical detail, whereas the low frequency probe guaranteed the definition of more deep seated abnormalities, such as the presence of the US trans-mantle sign (Fig. 1). Switching between higher and lower frequency probes could lead to better evaluation of deep seated white matter abnormalities at the cost of longer scanning times and a slight increase of both procedure cost and infection rate. Compared to intraoperative MRI (ioMRI), ioUS is less time consuming, even when switching between higher and lower frequency probes. Therefore, probe switching should be considered in all cases of type IIb FCD, particularly when the trans-mantle sign has been identified on the preoperative MRI.

IoUS demonstrated a sharper distinction of the grey-white matter junction when compared to MRI. At the pathological evaluation, type IIb FCD shows an indistinct grey-white matter transition [3], however the junction is blurred only at certain points [20]. Moreover, FCD demonstrate a gradual, rather than a sharp, demarcation between the dysplastic and the surrounding healthy brain tissue. In our small cohort study a high frequency ioUS evaluation depicted the lesions' lateral boundaries with a sharper contrast than MRI as judged by the observers in a qualitative setting. In all three patients who needed a wider area to be resected based on EcoG evaluation, there was a better correlation between this finding and the ioUS finding, rather than with that of the preoperative MRI. Those two findings could be due to higher ioUS spatial resolution and the absence of MRI partial volume effects, which inevitably affect both grey-white matter differentiation and the evaluation of the lesion's boundaries. High frequency probes reduce

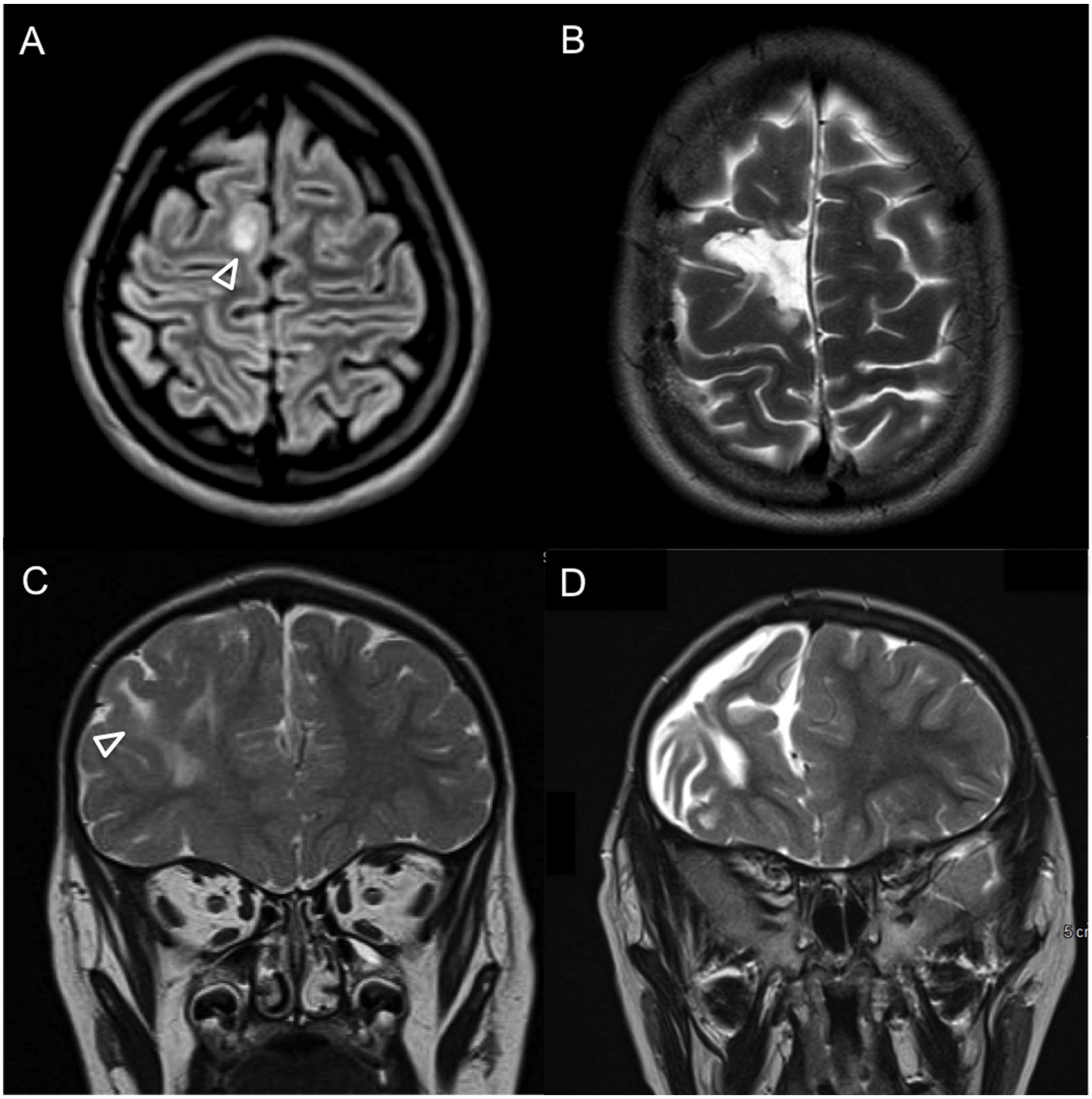

Fig. 4. Comparative post resection MRI.
Axial FLAIR (A) and T2 weighted images (B) showing the radical extent of resection in a patient with white matter hyper-intensity (empty arrowhead in A). Comparative para-coronal T2 weighted images (C, D) of another case before and after radical surgical excision of FCD. On the preoperative image subcortical white matter hyper-intensity (empty arrowhead in C) was visible.

wavelength and thus pulse duration. Compared to clinical MRI resolution (approximately 2–3 mm), the high frequency probe's axial resolution is much better (approximately 0.5 mm). Moreover, ioUS high temporal resolution (time from the beginning of one frame to the next) led to a reduction of partial volume effect [21].

4.2. Role of ioUS compared to other intraoperative techniques

Complete resection of the whole dysplastic area is directly related to surgical outcome [6] and freedom from seizure after surgery [5,22]. Eloquent areas require a tailored surgery to guarantee the widest resection possible without invalidating sequelae. Since, in these areas, a specimen from the adjacent region cannot be sampled for intraoperative histological analysis, no definitive resection-free margins from dysplastic changes can be guaranteed. FCD's ill-defined boundaries lead to 13% of patients undergoing a second-look surgery [23]. EcoG helps to define the epileptogenic zone, allowing for the identification of frequent or continuous paroxysmal activity (e.g. rhythmic spiking) [24] in cases with a rich interictal pattern. In deep seated (bottom of a sulcus) FCD, EcoG rarely depicts electrical activity.

IoMRI and neuronavigation's role in epilepsy surgery is undeniable, particularly in hardly recognizable lesions such as FCD, which lack visual and tactile differences between the dysplastic and adjacent normal brain tissue. Several studies demonstrated the feasibility, safety and ability of ioMRI to enhance the degree of removal and post-operative seizure control in FCD surgery, with consequent reduction of neurological deficits associated with eloquent cortex surgical damage [22,25]. On the other hand, ioMRI did not guarantee a spatial resolution comparable to preoperative studies. MRI neuronavigation is more accessible compared to ioMRI but is limited by intra-operative brain shift and deformation making pre-operative imaging unreliable in guiding surgical removal [26]. Moreover, neuronavigator volumetric images have lower pixel dimensions and therefore lower signal-to-noise-ratio compared to standard pre-operative images.

Therefore, ioUS could represent an optimal and agile adjunct imaging technique in FCD surgery, as highlighted in a previous paper from our group in which we described an integrated neurophysiological and image-guided surgical approach [19]. IoUS dynamic evaluation provides good image detail allowing for a paramount definition of surrounding structures, such as arterial and venous blood vessels, and of standard anatomical landmarks (dural structures, ventricles, choroid plexuses, and arachnoidal folds). Moreover, it has a higher spatial resolution compared to ioMRI and is independent from brain shift, providing high contrast detailed imaging. On the other hand, ioUS is not straightforward because it usually only permits the acquisition of oblique planes with a limited scan range. In our experience a combination between MRI neuronavigation and ioUS proved to be useful, with MRI facilitating lesion localization and probe orientation. Despite these drawbacks, in our population ioUS allowed for the detection of small and medium size FCD on multiple planes, giving tridimensional information on the dysplastic focus to the surgeon and allowing for a more confident resection.

4.3. Future perspectives

The high concordance between preoperative MRI and ioUS opens intriguing perspectives, leading the latter to be a valuable intraoperative tool. In addition, colour-Doppler, contrast enhanced US (CEUS) and elasto-sonography evaluation of FCD may guarantee acquisition of other paramount information [27,28]. If proved adequate, in the near future, ioUS could guide intra-operative resections, reducing the extent of the surgical field and unnecessary brain manipulation. Further studies comparing different ioUS aspects of various types of FCD may lead to discovery of essential information regarding their pathogenesis and similarities with other pathologies [2,29]. IoUS could be utilized in the evaluation of the surgical cavity, searching for unresected dysplastic zones prior to restoring the bone flap. In this scenario, new developments should be added to limit the presence and the extension of artefacts associated with the presence of air in the surgical cavity.

4.4. Limitations

The main drawbacks of this small study are the limited number of patient population and the relatively widespread differences in patient age and symptom duration. A long-lasting disease could therefore alter the anatomical and imaging characteristics of the dysplastic lesion.

5. Conclusion

Our study highlighted the potentials of ioUS as an intraoperative tool to detect and characterize FCD. Larger studies are warranted in order to confirm its clinical application and to define the appearance of other forms of FCD and their related features.

Conflict of interest

The authors declare that they have no conflict of interests.

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