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Original Article

Clinical and anatomical analysis of the epileptogenic spread patterns in focal cortical dysplasia patients

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ABSTRACT

Background: Focal cortical dysplasia (FCD) is one of the main causes of intractable epilepsy, which is amendable by surgery. During the surgical management of FCD, the understanding of its epileptogenic foci, interconnections, and spreading pathways is crucial for attaining a good postoperative seizure free outcome.

Methods: We retrospectively evaluated 54 FCD patients operated in Federal Center of Neurosurgery, Tyumen, Russia. The electroencephalogram findings were correlated to the involved brain anatomical areas. Subsequently, we analyzed the main white matter tracts implicated during the epileptogenic spreading in some representative cases. We prepared 10 human hemispheres using Klinger's method and dissected them through the fiber dissection technique.

Results: The clinical results were displayed and the main white matter tracts implicated in the seizure spread were described in 10 patients. Respective FCD foci, interconnections, and ectopic epileptogenic areas in each patient were discussed.

Conclusion: A strong understanding of the main implicated tracts in epileptogenic spread in FCD patient remains cardinal for neurosurgeons dealing with epilepsy. To achieve meaningful seizure freedom, despite the focal lesion resection, the interconnections and tracts should be understood and somehow disconnected to stop the spreading.

Keywords: Epilepsy, Focal dysplasia, Seizure spreading, White matter tract

INTRODUCTION

Focal cortical dysplasia (FCD) is one of the leading causes of medically intractable epilepsy during the first and second decades of life.[42] Resection of these lesions and their epileptogenic zones (EZs), offers a formidable solution in attaining meaningful postoperative seizure freedom.

Despite the modern magnetic resonance imaging (MRI) modalities, FCD lesion boundaries, particularly in FCD Type I and Type IIa, are often complex to delineate. It is, however, incumbent that neurosurgeons not only acquire a firm understanding of the focal lesions, but also of their potential epileptogenic spreading.

The existence of enhanced connectivity within the region of the lesion and ectopic EZs means a great challenge in the surgical management of patients with intractable epilepsy. Due to the EZ location within and beyond the perilesional boundaries, patients may show symptoms nonrelated to the primary dysplastic area, as interconnected epileptic networks play a cardinal role in the onset and propagation of ictal activity.[1] Therefore, physicians dealing with epilepsy patients should clearly understand the implication of those epilepsy networks, which in turn, will guide the extent of tissue resection (gross total or supramaximal resection). This will not only provide an adequate postoperative seizure relief, but will also account for perilesional and, in some instances, ectopic connectivity.

The process to accurately diagnose and localize the epileptic foci, with their epileptic zones, has greatly improved over the years. The cumulative use of invasive and noninvasive imaging techniques, patient's clinical presentation, and electroencephalogram (EEG) studies represents a cardinal component in the surgical management of FCD. Contemporary epilepsy surgery has shifted the paradigm into anatomical pathways of seizure spread. Therefore, it is not surprising the large number of reports highlighting the correlation between EEG findings and the involved anatomical areas, driving physicians dealing with epilepsy patients to gain an in-depth understanding of the implicated ictal and inter-ictal EZs.[22,23,35]

Thus, the understanding of the seizure spreading pathophysiology from the FCD areas through its EZ and even to more remote cortical areas[47] seems to be mandatory to adequately resect the epileptic foci, its epileptic zone, and interconnections. Acquiring a clear and sound understanding of the main white mater tracts offended between the lesion and its EZ connections appears as a valuable tool for neurologists, neurophysiologists and neurosurgeons dealing with epilepsy patients. The main goal of our study is to describe the clinical features and surgical results of a series of FCD patients, providing an anatomical correlation through cadaveric images, with a special effort to elucidate their relationship and the white fibers connections between FCD foci with their correlative ectopic EZs.

MATERIALS AND METHODS

Patients

We retrospectively analyzed the clinical records, as well as the pre and postoperative MRI images of a series of 54 FCD patients admitted for surgery due to intractable epilepsy at the Federal Center of Neurosurgery Tyumen, Russia, from September 2020 to July 2021. Ten out of those 54 patients were selected as the most representative cases to describe their clinical, electrophysiological, surgical, and anatomical features.

EEG evaluation

Patients were evaluated by an experienced neurophysiologist using long-term video EEG monitoring, through either a Nicolet One 32-channel device (stationary) (USA), bedside EEG system Nicolet ONE 16-channel and 32-channel (USA) device, a BE Plus (128-channel) EBNeuro/Ates (Italy) device, a Cadwell Easy III 64-channel device (USA), or invasive video-electrocorticography-monitoring. Ictal and inter-ictal recordings were then saved, evaluated, and interpreted. The aim of the detailed evaluation, together with other tests, was to identify the kind of seizures (generalized vs. focal vs. multifocal) and to determine the seizure onset zone (SOZ). The following key areas were also sought for: (1) SOZ, (2) irritative zone, (3) symptomatogenic zone (area that produces ictal symptoms), (4) functional deficit zone – interictal (functionally abnormal area), and (5) eloquent cortex – area of highly functional cortex.

Presurgical evaluation

All patients were symptomatic for FCD with confirmed resistance to anti-epileptic drugs (AED). A strict presurgical protocol included a specialized evaluation by neuroepileptologists, neuropsychiatrists, pediatricians, and neuroradiologists. Informed consent for surgery was obtained. A preoperative 1.5 Tesla MRI was routinely acquired in all FCD patients. In case, a more precise imaging evaluation was required, 3.0 T MRI studies were performed. The following MRI features were particularly sought: local thickening/thinning or atrophy of cortex, blurred borders between gray and white matter, presence of irregularly shaped gyri, heterotopy (shifting of gray matter towards the ventricles), transmantle dysplasia (the spread of gray matter activity to the brain ventricles through white matter fibers), hypo-intensity of the signal from white matter on T1-weighted imaging, hyper intensity of the signal from white matter on T2 and fluid attenuated inversion recover modes, complex "expansion of the subarachnoid space, and spreading deeper into the cortex." MRI baring the listed features was regarded as "MRI Positive," while MRI was considered "Negative" when images showed no obvious lesions.

Surgery

All procedures were carried out by the first author. A frameless navigation system was used to delineate the

optimal craniotomy in each case. Microsurgical removal of epileptogenic tissue was performed; under the guidance of intraoperative ultrasound (iUS). The FCD areas were identified as hyper-echoic relative to the healthy brain tissue, with uneven, fuzzy, and irregularly-shaped contours, by iUS. The use of iUS had the following main objectives: (1) localize dysmorphic brain tissue before and after opening the dura mater, due to shifting of anatomical structures once the dura is opened, (2) localize the pathological focus, (3) determine the structure and echogenicity of dysplastic tissue in relation to the surrounding normal brain, (4) delineate the contours of the abnormal/pathological tissue; (5) measure the dimensions of dysplasia; and (6) evaluate the effectiveness of the iUS to accurately delineate the area of resection, to optimize postoperative outcome. The FCD located within eloquent areas and involving white matter tracts within the EZ was safely resected and disconnected using multiple subpial resection techniques, with the aim of transecting the associative connections, trying to spare the projection fibers and vessels intact, and therefore increasing the chances of preserving the cortical function. Cortical mapping was carried out when the FCD was located close to highly functional areas, based on anatomy and clinical symptoms. Patients were followed up at 1st, 3rd, 6th months, and 1 year after surgery.

Correlation between EEG and anatomical areas

A correlation between the ictal and interictal EEG registered patterns and the involved anatomical areas was performed for each of the 54 cases included in the study, and based on the previous published data[22,23,26] [Table 1 and Figure 1]. The FCD area as well as the spreading zone and direction was electrophysiologically identified and categorized. Based on this information and the imaging anatomical features, the FCD and EZ were anatomically named as well as the potential most probable spreading pathways through the underlying white matter tracts theoretically connecting the involved cortical regions. We sampled patients with similar implicated representative tracts into groups and illustratively depicted 10 of them through the cadaveric dissections.

Diffusion tensor imaging (DTI) methodology and description

A male right-handed patient was evaluated using a 1.5 T MRI epilepsy protocol. DTI-MRI in axial planes was also included in the study. The tractography of each tract was reconstructed using the iPlanet/BrainLab software. Afterward, the 3D reconstruction of the brain and each of the tracts were displayed, using the BrainLab workstation to illustrate the most common tracts involved on the epileptogenic activity spreading in our series.

Cadaver preparation and dissection

After seeking institutional approval, 10 cadaveric hemispheres were harvested during autopsy for teaching purposes. All 10 hemispheres were obtained after immersion in a 10–15% formalin solution for a minimum period of 4 weeks. After arachnoid and vessels removal, the brains were frozen during 2 weeks (−18°C). The selected cortical regions were marked and the white fiber tracts were dissected using the fiber dissection technique, aided by an exoscope (Karl Storz 4K 3D VITOM exoscope) and microscope (Carl Zeiss OPMI Vario S8 Microscope) [Figure 2].

RESULTS

Patients' evaluation and surgery

Of the 10 patients included, six patients were female (60%) and four were male (40%). The mean age was 10.42 years (Standard Deviation ± 7.63). All patients were symptomatic for FCD, taking 2 or more AED without seizure relief. MRI was positive for FCD in all cases studied. EEG ictal and interictal evaluation (scalp and invasive) was performed in each case, confirming the origin and spread of the epileptiform activity in each of them. All patients underwent surgery, performing lesionectomy plus corticectomy with disconnection of fibers connecting to white matter tracts in seven cases, temporal lobectomy in two patients, and callosal disconnection in one case. The basal features, symptoms, AED, MRI results, EEG recording, type of surgery, and functional outcome (employing Engel scale) are summarized in Tables 1 and 2.

Anatomical–electrophysiological correlation

A correlation between the ictal and interictal EEG registered patterns and the involved anatomical areas has been performed for each patient [Table 2].

Case 1: "U" Fibers spread

In Case 1, the EEG showed an epileptogenic activity focus in the middle frontal gyrus (MFG), spreading to the superior and inferior frontal gyri, suggesting U-fibers involvement, as these are connecting adjacent giry. The short association U-fibers connect adjacent gyri running just below the deepest parts of the sulci. It is through these connections networks that FCD EZ spreads to adjacent brain areas. They arise from a gyrus, curve 180° into the sulcus depth, and then subsequently terminate into the adjacent gyrus neurons. In the case of the MFG, the U-fibers connect it with the superior frontal, inferior frontal and precentral gyrus, and also with other intra-gyral MFG areas[20,33] [Figure 3].

Case 2: Inferior longitudinal fascicle (ILF) fibers spread

Case 2 EEG recorded epileptic foci in the right occipital pole (O2) and EZ probably spreading through the ILF to the

Table 1: Correlation between EEG electrodes and cortical anatomy.

EEG Electrode	Anatomical location	EEG electrode	Anatomical location
Fp1	L superior frontal gyrus	Fp2	R middle/superior frontal G
F3	L MFG	F4	R MFG
F7	L IFG (TP)	F8	R IFG (TP)
C3	L precentral/postcentral gyrus	C4	R precentral/postcentral Gyrus
T3	L middle/STG*	T4	R middle/STG*
T5	L middle temporal G**	T6	R middle temporal G**
P3	L angular gyrus	P4	R angular gyrus
O1	L middle occipital G	O2	R middle occipital G
Fz	Supplementary motor area	Pz	Superior parietal lobe
Cz	Paracentral lobe		

L: Left, R: Right, *Rostrocaudal location-posterior to rolandic fissure, **Caudal to termination of sylvian fissure/posterior part, TP: Triangular part, IFG: Inferior frontal gyrus, STG: Superior temporal gyrus, MFG: Middle frontal gyrus, EEG: Electroencephalogram

right temporal lobe (T4, T6). The ILF is a long associative white matter tract that connects the anterior part of the temporal lobe to the occipital lobe and is composed by two components: a direct pathway and an indirect one. The indirect pathway is formed by U-shaped fibers that connect the adjacent gyri of the lateral occipitotemporal cortices to form the occipital-temporal projection system, described by Herbet *et al*.[21] Medial to these short association fibers, the direct pathway, composed of long association fibers, can be found. Connections of these white matter fibers with the anterior portion of the inferior, middle and superior temporal, parahippocampal, and fusiform gyri as well as the hippocampus and amygdala have been reported[13] [Figure 3].

Case 3: Frontal aslant tract (FAT) fibers spread

Case 3 illustrates a typical example of a FAT epileptogenic activity spread from inferior frontal gyrus (IFG) to superior frontal gyrus (SFG). The FAT connects the supplementary motor area (SMA) and pre-SMA in the SFG to the pars opercularis and pars triangularis in the IFG. The FAT has been described as an oblique bundle of white matter fibers that emerge within the superolateral aspect of the SFG, curving gradually in the inferolateral direction (about 90°) to terminate into the IFG. The FAT runs medial to the superior longitudinal fasciculus (SLF) on the lateral aspect of the cortex[31] [Figure 4].

Case 4: SLF fibers spread

Case 4 illustrates SLF-II implication in spreading epileptogenic activity from a primary FCD lesion located in the left precentral/postcentral gyri (C3) and left angular gyrus (P3), to the MFG (F3). The long association fibers of the SLF connect frontal and parietal cortical regions in the human brain. The SLF comprises of three distinct sub-bundles, each presenting different specific functional roles and anatomical trajectories. The SLF-I connects the superior parietal lobule and precuneus to the SFG and anterior cingulate areas. The SLF-II originates in the angular gyrus and anterior intraparietal sulcus and terminates in the posterior regions of MFG and SFG. The SLF-III, however, joins the intraparietal sulcus and inferior parietal lobule to the IFG[32,48] [Figure 4].

Case 5: Arcuate fascicle (AF) fibers spread

Epileptogenic spread through the AF from the primary FCD lesion epileptogenic foci located in the left superior and middle temporal gyrus (T3, T5), to the triangular part of the IFG (F7), was highlighted in Case 5. The AF is a peri-insular white matter tract that connects Broca's Area and Wernicke's Area through frontal, parietal, and temporal lobes[17,48] [Figure 4].

Case 6: Uncinate fasciculus(UF) spread

Primary epileptogenic foci (FCD) in the temporal lobe may produce excitable epileptogenic spread through the UF as illustrated in Case 6. The EEG in-depth epileptogenic spread was traced from the right medial temporal lobe to the right IFG (F8). The UF is a C-shaped white matter pathway that connects orbitofrontal cortex with the anterior temporal lobe. Although the UF cortical associations are still a matter of debate, it has been described that it connects with temporal and frontal poles, amygdala, hippocampus, orbital gyri, subcallosal area, gyrus rectus, IFG, and anterior temporal convexity.[33,34] The UF forms part of the ventral portion of the extreme and external capsule and its fibers intermingle at this level with some fibers of inferior frontal occipital fasciculus (IFOF)[9,45] [Figure 5].

Case 7: IFOF fibers spread

In Case 7, invasive EEG subdural electrodes depicted generalized discharges with a predominance of severity on the right occipital lobe (O2) with spread to the frontal lobe, suggesting an involvement of the IFOF. The IFOF is a long

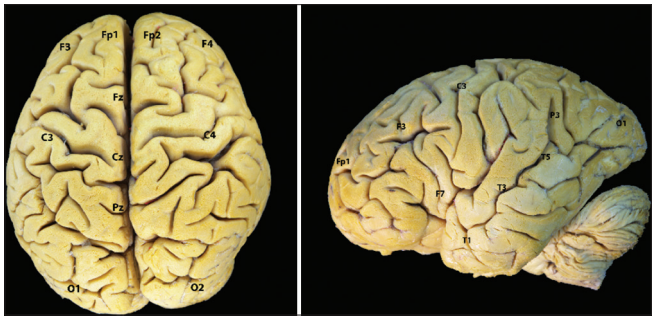

Figure 1: Correlation between electroencephalogram electrodes and cortical anatomy. Superior and lateral view of the brain surface (left side). Fp1: L Superior frontal gyrus, F3: L Middle frontal gyrus, F7: L Inferior frontal gyrus (TP), C3: L Precentral/Postcentral gyrus, T3: L Middle/Superior temporal gyrus*, T5: L Middle temporal gyrus, P3: L Angular gyrus, O1: L Middle occipital gyrus, Fz: Supplementary motor area, Cz: Paracentral lobe, Fp2: R Middle/Superior frontal G, F4: R Middle Frontal gyrus, F8: R Inferior Frontal gyrus (TP), C4: R Precentral/Postcentral gyrus, T4: R Middle/superior temporal gyrus*, T6: R Middle temporal G **, P4: R Angular gyrus, O2: R Middle occipital gyrus, Pz: Superior parietal gyrus, L: Left, R: Right, *: Rostro-caudal location-posterior to rolandic fissure; **: Caudal to termination of sylvian fissure/posterior part. TP: Triangular part

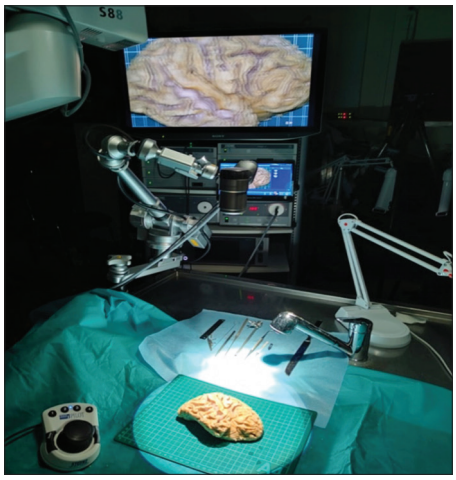

Figure 2: Exoscope-guided cadaveric dissection, with 3D camera.

white matter associative tract that connects the prefrontal area and orbitofrontal cortex directly to the parietal, occipital, and posterolateral temporal lobes. The IFOF can be divided in 3 main segments: (1) a vertical segment that arises from the mid part of MFG and runs along the frontal lobe, (2) a horizontal segment that arises from pars orbitalis and triangularis of IFG and also runs along frontal lobe, and (3) a horizontal segment that courses from the limen insulae, travels into to the temporal stem and reaches the parietal and occipital lobes. IFOF, in the insular segment, composes the ventral part of the external capsule, while the dorsal part is composed by the claustrocortical fibers.[2,16] The horizontal

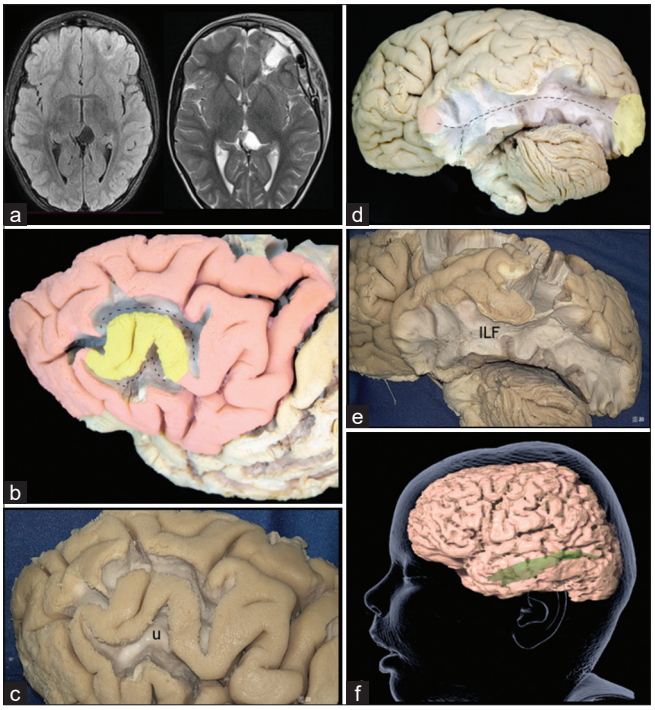

Figure 3: (a) Preoperative and postoperative maganetic resonance imaging (MRI) in a patient with focal cortical dysplasia (FCD) located in the left middle frontal gyrus (MFG). (b) Lateral view of the left frontal lobe, after dissecting of the U-fibers around the MFG. The epileptogenic zones (EZ) spread from the MFG to the inferior frontal gyrus and superior frontal gyrus through the U-fibers. Yellow: primary FCD EZ, Red: ectopic EZ, Discontinuous line: U-fibers. (c) Lateral view of the left frontal lobe, after dissecting the U-fibers around the MFG. u: U-fibers. (d) Lateral view of the left hemisphere, after removing the gray matter and U-fibers, exposing the ILF, which connects the EZ located in the occipital pole with the superior and medial temporal gyrus. Yellow: primary FCD EZ, Red: ectopic EZ. Discontinuous line: ILF. (e) Lateral view of the left hemisphere, after dissecting the ILF. ILF: Inferior Longitudinal Fascicle. (f) Tractography of the ILF.

portion of the IFOF runs superior and lateral to the optic radiations, traveling superolateral to the temporal horn, atrium, and occipital horn of the lateral ventricle [Figure 5].

Cases 8 and 9: Corpus callosum (CC) fibers spread

In Case 8, EEG confirmed epileptogenic foci from the left frontal lobe (Fp1, F3), bilateral-synchronously, with epileptic foci in the right frontal lobe (Fp2, F4), suggesting spread through the forceps minor of the CC. In Case 9, an invasive stereotactic deep EEG reveled epileptogenic activity in the left and right parietal lobes (C3 and C4, respectively). Therefore, the spread to the contralateral parietal lobe was most likely mediated through the superior or dorsal radiations of the CC. The CC is the primary white matter commissural tract. Its pathway connects the occipital, temporal, parietal, frontal, limbic, insular lobes, and the basal ganglia of both

hemispheres. Anatomically, from its anterior to posterior border, the CC is subdivided in five parts: rostrum, genu, body, isthmus, and splenium.[8] According with Shah *et al*., fibers of CC can be divided in four types: (1) fibers that cross laterally and come into the medial surface of the brain and after that curve upward, forming the superior or dorsal radiations of the CC, (2) the ventral or inferior CC radiations, which run laterally from the body and the genu of CC and then curves inferiorly, (3) the forceps minor or anterior radiations of the CC, traveling from the rostrum and the genu of CC anteriorly to the basal and medial frontal area as depicted in Case 8, and (4) the forceps major or posterior radiations of the CC, which run posteriorly from the splenium of CC and come into the medial surface of the occipital cortex[39,40] [Figure 6].

Case 10: Middle longitudinal fascicle (MdLF) fibers spread

In Case 10, invasive EEG considered a primary lesion in the superior temporal gyrus (STG) (T4), with suggestive spread to the postcentral and precentral gyri (C3), angular gyrus (P3) and the superior parietal lobe (Pz). Therefore, the FCD epileptogenic spread was somehow partially mediated through the MdLF. The MdLF is a long association pathway that runs in the lateral aspect of the brain and connects the STG with the parietal and occipital lobes. The MdLF travels through the anterior part of the STG and superior temporal sulcus area and under the U-fibers and the SLF/AF at the posterior temporal and inferior parietal lobes (anterolateral to posteromedial direction). It connects the STG to the superior parietal lobe and parietooccipital zone by running through the Transverse Gyri of Heschl; and the STG to the posterior area of the occipital cortex through the angular gyrus[16] [Figure 7].

DISCUSSION

Even though epilepsy surgery offers good postoperative seizure remission in FCD patients, adequate management of these cases is a daunting task.[44] This is because primary FCD lesions have closely linked EZ inter-connectives, through which seizures may spread.[28,41] The EZ is seen as complex structure composed of primary foci, relay, and subrelay areas essential to produce individual ictal symptoms and signs resulting in characteristic seizure

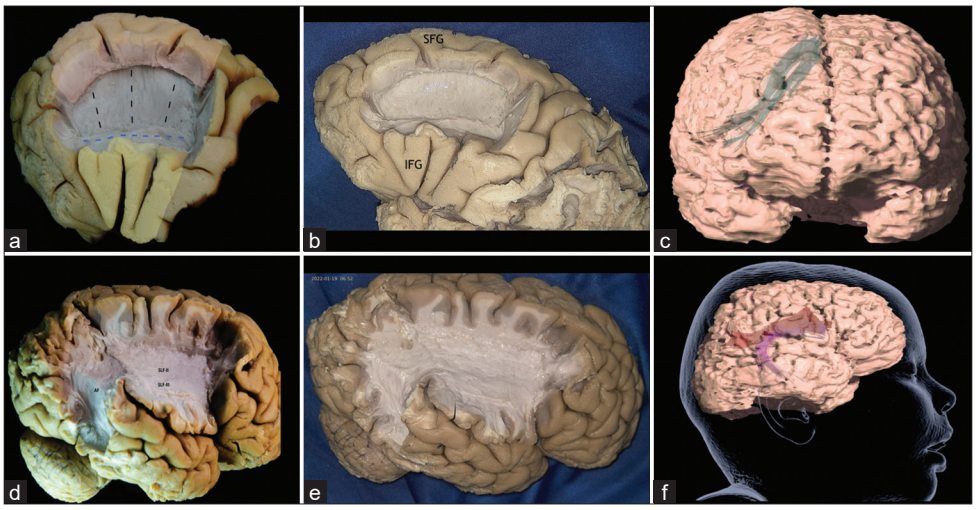

Figure 4: (a) Left frontal lobe after removal of the U-Fibers and part of SLF-II in the middle frontal gyrus, exposing the Aslant tract, which connects the supplementary motor area (SMA) and pre-SMA in the superior frontal gyrus to the pars opercularis and pars triangularis of the posterior inferior frontal gyrus. The inferior part of the SLF-II, which runs lateral to the aslant tract, is partially conserved. Yellow: primary focal cortical dysplasia epileptogenic zones (EZ), Red: ectopic EZ, Discontinuous black line: Aslant Tract, Discontinuous blue line: SLFII. (b) Left frontal lobe, exposing the Aslant tract. SFG: Superior frontal gyrus, IFG: Inferior frontal gyrus. (c) Tractography of the Aslant Tract. (d) Lateral view of the right hemisphere, after removal U-fibers of the middle and inferior frontal gyrus, inferior parietal lobe and the posterior part of the superior and middle temporal gyrus, exposing the SLF-II (originates in the angular gyrus and anterior intraparietal sulcus and terminates in the posterior regions of middle and superior frontal gyrus), SLF-III (joins the intraparietal sulcus and inferior parietal lobule to the inferior frontal gyrus), and the AF (connects Broca's Area and Wernicke's Area through frontal, parietal, and temporal Lobes). SLF-II: Superior longitudinal fascicle segment II, SLF-III: Superior longitudinal fascicle segment III, AF: Arcuate Fascicle. (e) Right frontal lobe, exposing the SLF-II, SLF-III, and the AF. (f) Tractography of the SLF-II and AF.

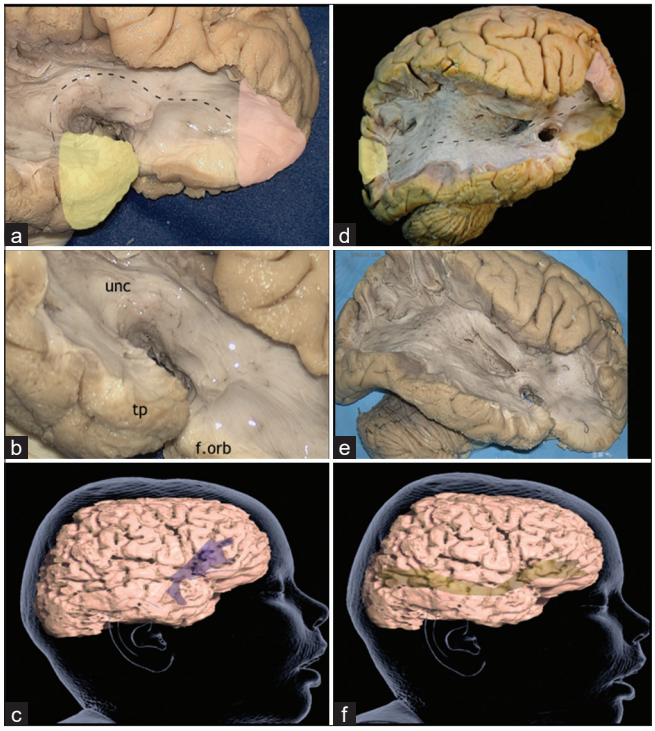

Figure 5: (a) Lateral view of the right temporal and frontal poles, after exposing the uncinate fascicle, which connects the orbitofrontal cortex to the anterior temporal lobe. Yellow: primary focal cortical dysplasia epileptogenic zones (EZ), Red: ectopic EZ, Discontinuous line: Uncinate fascicle. (b) Lateral view of the right frontal and temporal lobes, after the dissection of the Uncinate Fascicle. tp: Temporal pole, unc: Uncinate Fascicle, f.orb: Orbitofrontal cortex. (c) Tractography of the uncinate fascicle. (d) Lateral view of the right hemisphere after dissection of U-fibers of the frontal, temporal, parietal, and occipital lobes, insula and part of the extreme capsule, exposing the inferior frontal occipital fasciculus (IFOF), which runs from the prefrontal area and orbitofrontal cortex directly to the parietal, occipital and postero-lateral temporal lobes. In the same picture, the right Uncinate Fascicle and Anterior Commissure can be appreciated. Yellow: primary focal cortical dysplasia EZ, Red: ectopic EZ, Discontinuous blue line: Anterior Commissure, Discontinuous black line: IFOF, Discontinuous white line: Uncinate fascicle. (e) Lateral view of the right hemisphere, exposing IFOF, uncinate fascicle, and anterior commissure. (f) Tractography of the IFOF.

patterns.[30] In some instances, multiple epileptogenic foci may exist independently [Tables 2 and 3]. Due to this, poor postoperative seizure outcomes may be observed despite achieving a successful removal of the primary lesion.[18] The lack of a clear understanding of the epileptogenic foci and spreading pathways can lead to suboptimal resection of the lesion and subsequently to unfavorable postoperative seizure control [Table 2]. Therefore, an adequate understanding of the potential pathways through which seizures spread in FCD patients can highly enhance the clinical intervention in terms of, neurostimulation, neuromodulation, and resection.[38]

The epileptic zone and white matter tracts

Seizure networks generally start from the EZ which has within itself a SOZ. The SOZ can be the dysplastic area of the cortex from which clinical seizures actually arise.[3] Thus, the EZ can be more extensive than the SOZ itself. Seizure spreading patterns in the brain have been closely associated with white matter structural brain pathways. The diseased and afflicted connecting fibers of white matter tracts in FCD are a major factor in epileptic networks and must be considered in the surgical management.[10,15] The seizures spread of the epileptic discharge is not random, but follows preferential pathways.[43] Gleichgerrcht *et al.* managed to demonstrate distinctive intricate relationship and directional epileptogenic spread through white matter tracts.[18] In their study, patients with temporal lobe epilepsy (TLE) were observed to have seizure spreading through medial-lateral axis (cingulate and CC) or evolving on an anteroposterior axis (uncinate fasciculus, IFOF, or AF). Overlapping of anatomic networks is also likely to be affected by the duration of epilepsy. An epileptic longer duration leads to greater disruption of functional neuroanatomical cognitive networks, enchanting epilepsy networks, and reducing the likelihood of seizure freedom or neuropsychological improvement following surgical treatment.[10,18,36]

The symptomatogenic zone

The symptomatic zone produces the initial ictal symptoms.[7] Due to interconnections within the epileptogenic foci and spread, it may be noted that the presenting symptom may not be typically representative of the symptomatogenic and the EZ. The ictal signs and symptoms are often triggered by excitation from an EZ located in a symptomatically "silent" distant area.[4] For example, in Case 2, the patient presented with symptoms related not only to occipital lobe involvement (visual hallucinations), but also symptoms typically related with the frontal lobe epilepsy (facial and oral automatism) [Tables 2 and 3]. On the other hand, in Case 7, invasive EEG subdural electrodes depicted discharges on the right occipital lobe (O2), but the patient presented symptoms related to frontal lobe involvement, as focal seizures and alexia. Explanation to this phenomenon is possibly the result of epileptogenic spread through the ILF and inferior Fronto-occipital fascicle, respectively.[2,16]

Moreover, some patients present symptomatology that could be related with the overexcitement or dysfunction of some white matter tracts.[29] In Case 6, it was possible to observe postictal episodes of amnesia, which is typically related with uncinate fascicle dysfunction. Otherwise, in Case 3, patient displayed symptoms of autism and severe development delay which could be related with FAT dysfunction.[6,14,31]

Table 2: Basal characteristics, symptoms, AED, MRI results, EEG recording, type of surgery, and functional outcome (employing Engel scale).

Patient	Sex	Age years	Symptoms	AED	MRI	EEG evaluation (epileptogenic foci/spread)		Surgery	Engle outcome
1	F	0	• Generalized tonic-clonic seizures up to 10 times per day	• Carbamazepine • Lamotrigine	L MFG FCD lesion	F3	Fp1, F7	Microsurgical L lesionectomy	I
2	F	8	• "Deja vu" of horrific events (visual hallucinations) • Strange voices • Facial and oral automatism • Tonic and generalized seizures 3 times/week	• Levetirazetam • Carbamazepine • Valproic	R occipital FCD lesion	O2	T4, T6	Microsurgical R occipital lesionectomy	I
3	M	4	• Myoclonic fits 6 times per day • Severe developmental delay • Autism	• Levetirazetam • Vigabatrin • Valproic	L frontal FCD lesion	F7	Fp1	Microsurgical L frontal lesionectomy	II
4	M	23	• Simple seizures presenting as hallucinations and illusions. • 20 times/day • Tonic-clonic seizures 5–6 times/month	• Carbamazepine • Lamotrigine	L parietal FCD lesion	C3, P3	F3	Microsurgical L lesionectomy+subpial transection	I
5	M	22	• Worsening illusions and absence from reality, place and time • Anxiety feelings, palpitations without loss of consciousness • 10–12 times/day	• Valproic • Lamotrigine • Carbamazepine	L temporal FCD lesion	T3, T5	F7	L temporal lobectomy	I
6	F	8	• Flexor myoclonus seizures • 5–6 times/day • Postictal amnesia	• Levetirazetam • Vigabatrin • Valproic	R temporal pole FCD lesion	T4	F8	R Anterior Temporal Lobectomy.	II
7	M	3	• Focal seizures. ≥9–10/day Aprexia	• Levetirazetam • Vigabatrin • Valproic	R parieto-occipital FCD region	O2	Subdural (frontal lobe)	R occipital lesionectomy	I
8	F	10	• Myoclonic seizures 5–7/day • Sudden changes in personality	• Levetirazetam • Carbamazepine • Valproic	L frontal pole FCD lesion	Fp1, F3	Fp2, F4	Microsurgical L frontal lesionectomy	I
9	M	11	• Tonic-clonic seizures≥3/day • Drop attacks	• Levetirazetam • Valproic	L parietal lobe FCD lesion	C3	C4	Corpus callosum disconnection	II
10	F	15	Tonic-clonic fits which began with taste aura 9–10 times/day	• Carbamazepine • Lamotrigine	R temporal lobe dysplastic lesion	T4	C3, P3, Pz	Microsurgical R temporal lesionectomy	I

AED: Anti-epileptic drugs, FCD: Focal cortical dysplasia, MFG: Middle frontal gyrus, MRI: Magnetic resonance imaging, L: Left, R: Right, EEG: Electroencephalogram, M: Male, F: Female

Surgery

To reduce the seizure burden and potentially improve cognitive function, a holistic and well encompassing FCD surgery must involve the total resection of the lesion, as well as its complete disconnection from the connecting fiber networks and EZ.[11,27,39] In this study, resective surgery management was the main stay treatment. The technique used an iUS-guided lesionectomy with corticectomy and multiple subpial transections in regions of close proximity to eloquent ictal areas.[5] This methodology entailed complete resection of the offending lesion and disconnection of the afflicted fibers from white matter tracts. A perilesional corticectomy (0.5–1) cm was performed to encamp the epileptic zone and inter epileptogenic connectivity.[13]

The anterior temporal lobectomy followed by an amygdalo-hippocampectomy provided with a good postoperative outcome, especially in patients operated for FCD (II a – II b). We considered that FCD TLE afflicts not only the insulted cortex but also the white matter tracts within epileptogenic area, such as, the uncinate fascicle, the parahippocampal fibers, and the inferior frontolongitudinal fasciculus. After lateralizing the FCD, our limits of resection in the nondominant hemisphere extended 4–5 cm from the temporal pole on the STG and 3–5 cm in the language dominant one. Where we faced close typical speech eloquent zone lesion boundaries, multiple sub-pial transections were carried out to isolate the epileptic focus from the adjacent cortex.

The basis of performing a corpus callosotomy in our patient in Case 9 was generalized epileptogenic spread and drop attacks as highlighted in Table 1. This was done to prevent the interhemispheric seizure spreading [Figure 6]. The surgical technique of the anterior two-thirds callosotomy was performed in the traditional way (approximately 2 cm precoronally and 5 cm retrocoronally).[19] After the craniotomy, a meticulous dissection of the interhemispheric fissure till reaching the CC was performed. Consequently, the callosotomy without anterior commissure disconnection was performed.

It must be clear that even though we advocate for extensive and safe FCD lesion- EZ resection with the aim of achieving seizure control, white matter tracts function must be preserved. Where lesions are located near eloquent areas, functional monitoring is always highly recommended and even awake surgery could be considered in much selected cases.[24,25]

Future considerations

Recently, aspects for lesser invasive and effective methods of lesion resection have been taking center stage. Stereotactic laser

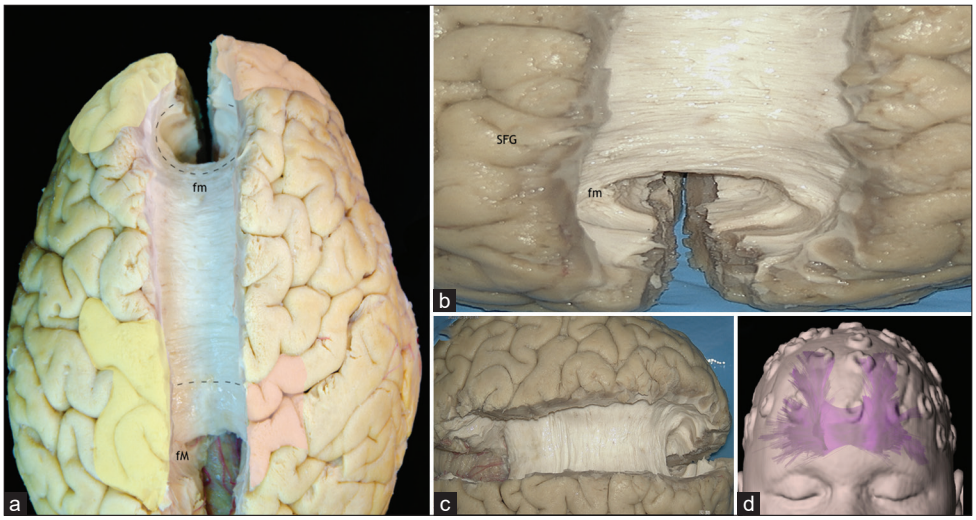

Figure 6: (a) Superior view of both hemispheres, after removal of the cingulum and the U-fibers of the medial surfaces, exposing the dorsal radiations of the corpus callosum (CC), the forceps major or posterior radiations and the forceps minor or anterior radiations. Yellow: Primary focal cortical dysplasia epileptogenic zones (EZ), Red: ectopic EZ, Discontinuous line: Commissural fibers of the CC, fm: Forceps Minor, fM: Forceps Major. (b) Superior view of both frontal lobes, after removal of the cingulum and the U-fibers of the medial surfaces, exposing the forceps minor or anterior radiations of the CC, which connects the medial surface and the basal region of both hemispheres. fm: Forceps minor, Superior frontal gyrus. (c) Superior view of both hemispheres, after removal of the cingulum and the U-fibers of the medial surfaces, exposing the dorsal radiations of the CC, the forceps major or posterior radiations and the forceps minor or anterior radiations. (d) Tractography of the CC. SFG: Superior frontal gyrus

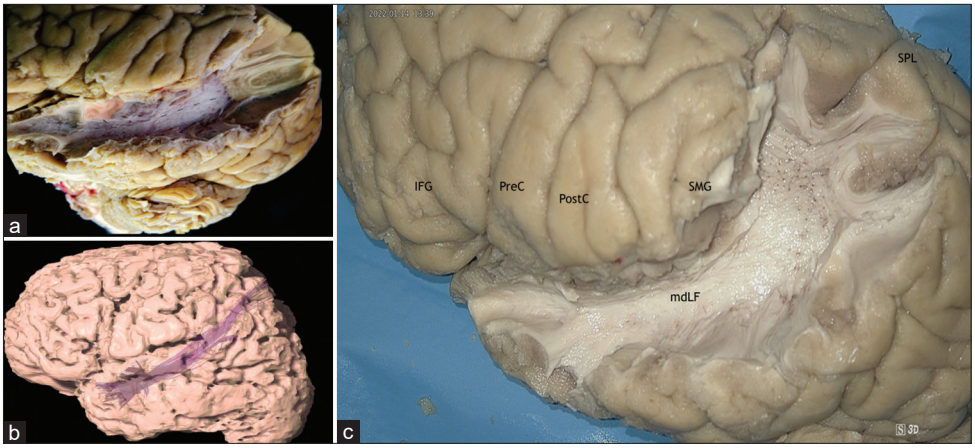

Figure 7: (a) Lateral view of the left hemisphere after the removal of the U-fibers, superior longitudinal fasciculus, and arcuate fascicle, exposing the mdLF. The mdLF connects the superior temporal gyrus with the parietal and occipital lobes. Yellow: primary focal cortical dysplasia EZ; Red: ectopic EZ; Discontinuous line: mdLF. (b) Tractography of the mdLF. (c) Lateral view of the left hemisphere, after dissection of the mdLF. mdLF: Middle Longitudinal Fasciculus, SPL: Superior Parietal Lobe, IFG: Inferior frontal gyrus, PreC: Precental gyrus, PostC: Postcentral gyrus, SMG: Supramarginal Gyrus, EZ: Epileptogenic zones, and SLF: Superior longitudinal fasciculus.

Table 3: Anatomical–electrophysiological correlation.

Patient	EEG evaluation		Anatomical correlalation	
	Epileptogenic Foci	Spread area	Epileptogenic Foci	Spread area
1	F3	Fp1	L MFG	L SFG
		F7		L IFG (TP)
2	O2	T4	R middle occipital G	R middle/STG*
		T6		R middle temporal G**
3	F7	Fp1	L IFG (TP)	L SFG
4	C3	F3	L PreC/PostC	L MFG
	P3		L angular gyrus	
5	T3	F7	L middle/STG*	L IFG (TP)
	T5		L middle temporal G**	
6	T4	F8	R middle/STG*	R IFG (TP)
7	O2	Subdural (frontal lobe)	R middle occipital G	R frontal lobe
8	Fp1	Fp2	L SFG	R middle/superior frontal G
	F3	F4	L MFG	R MFG
9	C3	C4	L PreC/PostC	R PreC/PostC
10	T4	C3	R middle/STG*	L PreC/PostC
		P3		L angular gyrus
		Pz		Superior parietal lobe

IFG: Inferior frontal gyrus, MFG: Middle frontal gyrus, STG: Superior temporal gyrus, SFG: Superior frontal gyrus, L: Left; R: Right, TP: Triangular part, EEG: Electroencephalogram, PreC: Precental gyrus, PostC: Postcentral gyrus, *: Rostro-caudal location to rolandic fissure, **: Caudal to terminaton of sylvian fissure/posterior part

ablation (SLA) for FCD offers promising prospective results, similar to open surgery cases.[37,46] With SLA, we hope to delve into aspects of minimally invasively targeting epileptogenic foci, its EZ, and interconnections with the least morbidity and best seizure free outcome.[12] We hope that in future, large SLA for FCD prospective studies can be done to assess the postoperative seizure outcome in FCD with drug intractable epilepsy.

CONCLUSION

Understanding of the main implicated tracts in the epileptogenic spread in FCD patient remains cardinal for all those physicians dealing with epilepsy patients. To achieve seizure freedom, not only should the focal lesion be resected, but also its interconnections and tracts. It is therefore highly recommended that during EEG evaluation of the EZ and

the ectopic foci, the main white matter tracts implicated are identified.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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