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Focal cortical dysplasias

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ABSTRACT
Focal cortical dysplasias (FCDs) are localised malformations of cortical development, often associated with refractory epilepsies. Seizure onset most commonly occurs in the first decade of life and the clinical presentation varies according to the localisation of the lesion. Neuropsychological impairment often accompanies the high seizure burden, and can also be associated with the location and extent of FCD. Drug-resistant seizures can be controlled in a significant percentage of patients if adequate surgical treatment is possible. Although some clinical, electroencephalographic and neuroimaging characteristics of the FCDs are well understood, the differences among the histological subtypes of FCDs remains to be better determined.

Keywords: Focal cortical dysplasia; refractory epilepsy

INTRODUCTION
The focal cortical dysplasias (FCDs) are localised malformations of cortical development, classically associated with drug-resistant epilepsies. Taylor *et al*. originally introduced the term FCD in a study that described the histological findings of the focal cortical malformation [1]. In patients with FCD, the seizures most commonly begin in the first decade of life and may be refractory to antiepileptic drug treatment. In such cases, surgery with resection of the dysplastic lesion and the epileptogenic zone is the best option for seizure control. In children with focal epilepsies undergoing surgery, FCDs are the most common histological substrate [2].

HISTOLOGY AND CLASSIFICATION OF FCD
Since the initial description by Taylor *et al*. in 1971 [1], advances in the detailed knowledge of histology [3-5] has led to different proposals for classification of FCDs. However, considerable heterogeneity remained in the distinct descriptions of the histopathological findings by different authors [5]. Recently, the International League Against Epilepsy (ILAE) proposed an electro-clinical, imaging and histological classification for the FCDs [6]. This classification distinguishes isolated FCDs (types I and II) from FCDs associated with other potentially epileptogenic lesions (type III) (Table 1).

Table 1: ILAE classification system of focal cortical dysplasia (FCD)*

FCD type I	A	Abnormal radial cortical lamination
	B	Abnormal tangential cortical lamination
	C	Abnormal radial and tangential cortical lamination
FCD type II	A	Presence of dysmorphic neurons
	B	Presence of dysmorphic neurons and balloon cells
FCD type III		Cortical lamination abnormalities adjacent to hippocampal sclerosis (type IIIa), glial or glioneuronal tumor (type IIIb), vascular malformation (type IIIc) or any lesion acquired during early life (type IIId).

* Blumcke *et al*., Epilepsia 2011

According to the current ILAE classification, the FCD type I is defined by abnormal formation of cortical layers, which can compromise the radial neuronal migration and maturation (FCD type Ia) or tangential composition of the six layers of the neocortex (FCD type Ib). The concomitant occurrence of these two histological findings is classified as FCD type Ic [6]. The type II FCD is defined by disorganised cortical lamination and specific histological abnormalities that differentiate the FCD type IIa (presence of dysmorphic neurons without balloon cells) and FCD type IIb (presence of dysmorphic neurons and balloon cells) [6]. The type III FCD represents alterations in cortical lamination associated with an adjacent main lesion, this can occur in combination with hippocampal sclerosis, tumours, and vascular malformation amongst others [6]. This classification also suggests that the term “microdysgenesis” [7], used heterogeneously by different studies to describe subtle abnormalities of intracortical architecture, should be abandoned.

Histological characteristics of FCDs according to the ILAE classification:

The different types of FCDs have distinct cellular elements. As a group, the FCD histology presents focal brain areas with architectural abnormalities, immature or dysmorphic neurons and balloon cells [5]. The FCD type Ia (FCD with abnormal radial cortical lamination) is characterised by abundant micro-columnar organisation (more than eight neurons vertically aligned), more prominent inlayer 3. Cell abnormalities, such as small immature neurons or hypertrophic pyramidal neurons outside layer 5 can also be found [6]. The FCD type Ib (FCD with abnormal tangential cortical lamination) is characterised by failure in the tangential composition of the six layers of the isocortex. Small immature neurons or hypertrophic pyramidal neurons outside layer 5 can be found, as well as normal neurons with dendrites displaying irregular orientation [6]. In FCD type Ic, radial and tangential cortical lamination are both abnormal [6].

The FCD type IIa is characterized by the presence of dysmorphic neurons. Dysmorphic neurons are cells with aberrant shape, abnormal orientation, enlarged size, abnormal cytoskeletal structure and atypical dendritic processes. These cells have an accumulation of cytoplasmic neurofilaments [5,8]and there are no balloon cells present. Discrimination of the cortical layers, except for layer 1, is not possible [6]. Type IIb FCD is characterized by the presence of dysmorphic neurons and balloon cells. A balloon cell is an abnormal cellular structure with a thin membrane, eosinophilic cytoplasm and single or multiple nucleus. These cells have characteristics of both neurons and glia [5]. A detailed view of the cortical layers, except for layer 1, is not possible and the content of myelin may be abnormal in the adjacent subcortical white matter [6].

The FCD type III (changes of cortical lamination associated with an adjacent main lesion) can be classified into four variants: FCD associated with hippocampal sclerosis (type IIIa), FCD associated with tumours (type IIIb), FCD associated with vascular malformations (IIIc) or FCD associated with another main lesion acquired in early life [6].

PATHOGENESIS AND EPILEPTOGENICITY OF FCD

The current main hypothesis regarding the pathogenesis of FCD is that it results from an impairment of neuronal proliferation, differentiation, or migration. According to the 2012-updated Barkovich´s proposal of classification of malformations of cortical development, FCD type II is in fact a malformation due to abnormal proliferation and differentiation [9]. This classification is supported by the findings that FCD type II has progenitor proteins that appear early in development, similar to those found in pluripotent stem cells and due to the suggestion that balloon cells in FCD type IIb originate from glioneuronal progenitor cells [10,11]. Alternatively, FCDs type I and III are considered malformations due to abnormal post migration development. It is hypothesised that these may result from injury to the cortex during the late stages of cortical development [9]. Indeed, different studies have suggested the association of perinatal insults with the development of the dysplasias [12,13]. This concept suggests that FCD type I could be a heterogeneous group of disorders resulting from late insult to the developing cortex.

In vivo and ex vivo studies show that FCD has intrinsic epileptogenicity [14]. However, the intrinsic epileptogenicity of the dysplastic tissue varies according to the cell population. In vivo electrocorticographic recordings have shown that areas in the dysplasia containing balloon cells are less epileptogenic than the remaining dysplastic region [15,16]. The hypothesis in fact, is that balloon cells disrupt the structure of the surrounding cortex thus leading to excitability of the dysplastic tissue [17]. Distinctly, cytomegalic neurons show the most abnormal intrinsic electrophysiological properties [17]. In vitro studies have also shown an overall increase in expression of glutamate receptors and decreased expression of GABA receptors in surgical specimens of patients with FCD type IIb [8,18].

CLINICAL, ELECTROENCEPHALOGRAPHIC AND NEUROIMAGING CHARACTERISTICS OF FCD

Clinical characteristics of FCDs:

The true prevalence of FCD is unknown and the data from the current studies are mostly biased by specific selection criteria. Furthermore, the occurrence of FCD in any patient can only be confirmed by histological examination. In selected surgical series, up to 25% of drug-resistant epilepsies are secondary to confirmed FCD [4]. This varies from 23 to 78% of epilepsy surgical series in children to less than 5 % in adults [19,20]. However, the prevalence of FCD in patients excluded from surgical groups due to seizure control under antiepileptic drugs or surgery contraindicated, remains obscure.

As a group, FCD may occur at any anatomical location, and seizures can start at any age, however the onset usually happens in the first decade of life. The age of onset is particularly important in determining the clinical presentation. Patients with early onset have high seizure frequency and status epilepticus more frequently. Also, some series showed that early epilepsy onset is associated with a posterior localised or multilobar lesion [21]. Infants can present infantile spasms and/or focal seizures and older children characteristically present focal seizures. The semiology is stereotyped in each patient and depends on the localisation and extent of the lesion and the epileptogenic network [21]. Overall, the seizures are characteristically refractory to antiepileptic drug treatment. Few case-reports in the literature describe patients with FCD and seizure-freedom under antiepileptic drug treatment [22,23].

Other common clinical abnormalities in patients with FCD are behaviour disorders and intellectual disability, especially in patients with early seizure onset. In one series, 70% of patients with FCD presented a below average full-scale IQ [24]. Neuropsychological deficits are usually associated with early seizure onset and high seizure burden [6]; however, the localisation and extent of the lesion may also contribute to the deficit. The contribution of the use of antiepileptic drugs and the social disruption to the intellectual and behavioural impairments observed is poorly understood.

Some studies illustrate that up to one-fourth of the patients with histological confirmed FCDs had a history of head trauma or central nervous system infections [24]. This fact indicates that if the clinical features point towards FCD, it should be suspected even in cases with history of epilepsy risk factors.

There are still controversies on the differences of the clinical history, EEG and neuroimaging characteristics between the subtypes of FCDs. This predominantly originates from

the heterogeneity of histological descriptions among pathologists [6]. Currently a larger amount of clinical and neuroimaging data is available for FCDs type II than for type I. Patients with FCD type II experience seizure onset most commonly during childhood and high seizure frequency, including episodes of status epilepticus are present from the beginning [25,24]. In addition, extra-temporal localisation is more common in FCD type II. [25,26]. There is no clear data on the clinical differences of FCDs types IIa and IIb [24]. Some authors suggest that patients with type II FCD have a lower age of onset and higher frequency of seizures compared with patients with type I FCD [24,27], while other authors did not observe this difference [28]. Also, FCDs type IIa and IIb have different abilities to preserve function [16]. Eloquent functions are only present in the FCD areas without balloon cells and no increased signal in the MRI FLAIR images [15].

For FCD type I, some studies suggest that children have low intelligence, behavioural disorders [28-30], and multilobar involvement [30,31], Conversely for other authors FCD type I is most commonly found in adults and located within the temporal lobe [24,27]. Indeed, FCD type I is associated with cognitive impairment in patients with epilepsy, as well as in patients with autistic features and normal MRI [32].

The FCDs type III have the same type of clinical presentation and prognosis of the isolated main pathologies (for example, hippocampal sclerosis or tumour) associated with the dysplasia [31].

Electroencephalography and FCDs:

Electroencephalograms (EEGs) demonstrate the typical characteristics of FCD, which are more likely associated with type II dysplasias. The characteristic findings of scalp EEG in FCD type II are rhythmic focal interictal epileptiform discharges [33]. Recently, a distinctive scalp EEG pattern consisting of localised rhythmic or pseudo-rhythmic spikes or polyspikes ("brushes") was demonstrated to be increased during NREM sleep, to occur in about 40% of type II FCD's [25] and to be associated with the presence of balloon cells [26]. Invasive EEG recordings in FCD type IIb showed an absence of organised background activity and characteristic high amplitude fast repetitive discharges followed by high amplitude slow waves [14].

Neuroimaging and FCDs:

The introduction of MRI has facilitated the in vivo detection of FCD [6]. In MRI, some types of FCD are readily recognised, especially FCD type IIb, while many patients with histologically proven FCD have normal MRIs. This implies that many "MRI negative" focal epilepsies can be secondary to "hidden" FCD. Likewise, the ability to detect abnormal findings suggestive of FCD in MRI depends not only on the quality of the image and adequately chosen MRI sequences, but also on the experience of the neuroradiologist [34]. Therefore, it is currently difficult to determine the percentage of patients with FCD and normal MRI.

The FCD type II is the most easily recognised on MRI and is characterised by blurring of the cortico-subcortical junction and subcortical hyperintensity seen on T2-weighted / FLAIR images [35] (Figure 1). In some cases, a "transmantle" sign can be observed. This is characterised by a linear image hyperintense on T2-weighted and hypointense on T1-weighted images extending from a gyrus or sulcus toward the ventricle [36]. The transmantle sign is more often observed in FCD type IIb [37]. Other signs suggestive of FCD type II that can be observed from MRI are abnormalities in the anatomy of sulci and gyri and increased adjacent subarachnoid space [6,37]. It is a consensus that the FCD type IIb is easily recognised on MRI, whereas type IIa FCD may or may not show detectable changes [6,37]. A recent study suggests that the clinical and electroencephalographic characteristics of MRI-positive or MRI-negative histologically proven type II FCD is similar, with only a significantly higher frequency of sleep-related epilepsy in the former group [25]. Based on the pattern of MRI findings, some studies refer to transmantle dysplasias [36] and bottom of the sulcus dysplasias [38,39] as distinct entities, but both MRI findings share a good correlation with FCD type IIb histology [9]. Regarding FCD type I, some research has shown negative findings on MRI exams [31], while others describe subtle signs such as reduced ("hypoplastic") volume of the affected hemisphere [30].

The MRI appearance of FCDs may change during brain maturation, especially in young infants. This is due to incomplete myelination and lack of grey and white matter contrast; thus, it is often not possible to detect the abnormal characteristics of FCD in MRI [40]. However, the absence of myelination in the first months of life can also facilitate the detection of FCDs, which may be difficult to identify in later exams [41]. Therefore, on suspicion of FCD early scans may be useful but similarly a new MRI after two years of age might also be beneficial to add information previously missed.

Functional neuroimaging techniques also play an important role in the detection of abnormalities associated with FCD, especially for pre-surgical evaluation. A recent study with histologically proven FCD type II patients demonstrated that fluorodeoxyglucose positron emission tomography (FDG-PET) helped to localise the epileptogenic zone in 84% of patients with normal MRI and to delineate the dysplastic cortex in 64% of MRI-positive cases [25]. Additionally, one group showed that the use of 11C-alpha-methyl-l-tryptophan (AMT) on PET may predict type IIB FCD in those with increased AMT uptake [42].

TREATMENT OF EPILEPSY ASSOCIATED WITH FCD

There is no particular antiepileptic drug treatment for epilepsy related to FCD and the medication must be prescribed according to the specificities of each individual patient, such as seizure type, age, sex and comorbidities [43].

According to the ILAE, drug-resistant epilepsies can be defined as the failure of achieving seizure-freedom after two adequate trials of antiepileptic drugs [44]. Although there is no epidemiological data on the percentage of patients with FCD and drug-resistant epilepsies, it is current knowledge that the majority of patients will fulfil the criteria of drug-resistant epilepsy, most possibly in the first years after seizure onset. For those individuals, epilepsy surgery is the best treatment option. One should also bear in mind that both the refractory seizures and the cognitive and developmental impairment, must be considered for the indication of surgical treatment of children with FCD. Due to the high morbidity and psychosocial consequences associated with the refractory seizures, the identification of refractoriness and indication for surgical treatment, whenever achievable, should be performed as early as possible [45].

As it is the case for any epilepsy surgery, the final goal is achieving seizure freedom by the removal of the epileptogenic zone, defined as the extent of cortex necessary to generate the clinical seizures [46]. In order to accomplish

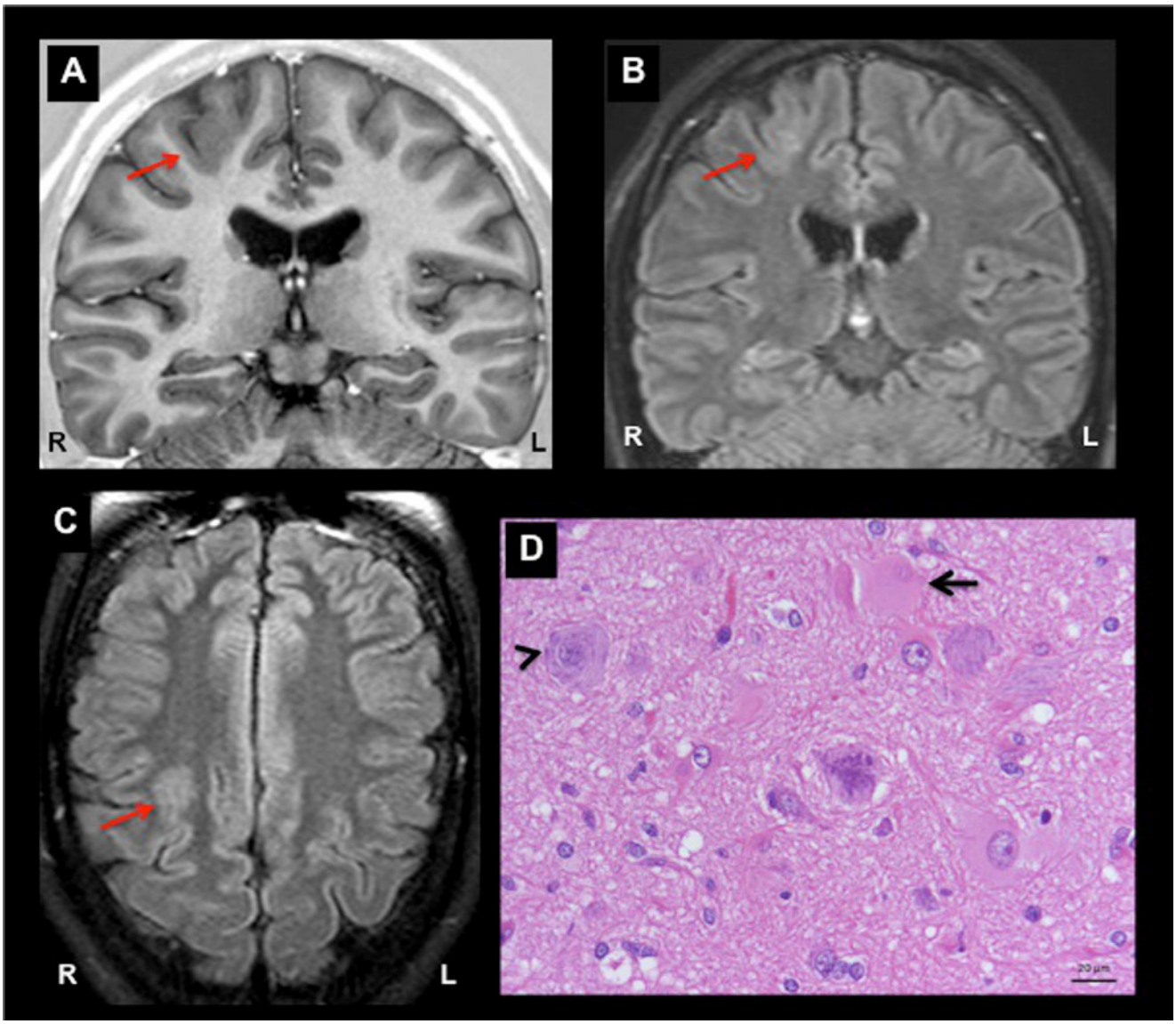

Figure 1: MRI and histology in focal cortical dysplasia type IIB.
MRI images (A, B, C) and **histology (D)** of a 15-year-old female patient with epilepsy onset at 5 years of age and drug-resistant seizures. After clinical, electroencephalography and neuroimaging evaluation, the patient was submitted to surgical resection of the suspect area of focal cortical dysplasia. She has been seizure-free since the procedure. The pre-operatory MRI showed blurring of the cortico-subcortical junction in the right frontal region in T1-weighted images (A, coronal slice) and increased signal in the same region in FLAIR images (B, coronal slice and C, axial slice) (red arrows). The histology of the surgical specimen (D; hematoxylin-eosin staining) showed dysmorphic neurons (black arrow head) and balloon cells (black arrows) in addition to abnormal cortical layering, consistent with type IIb focal cortical dysplasia.
MRI: magnetic resonance imaging; R: right side; L: left side.
Histological image courtesy of Dr. Fabio Rogerio (Pathology Department, Unicamp).

this objective an individual evaluation is necessary, including, at least, detailed semiology data, ictal and inter-ictal video-EEG monitoring and MRI. For some patients, other non-invasive (FDG-PET, ictal SPECT, MEG, functional MRI) or invasive (subdural EEG grids or depth electrodes) evaluations are necessary, especially for those with normal MRI or FCD in the proximity of eloquent cortex [47,48]. Therefore, patients with suspected FCD and drug-resistant seizures must be promptly referred to a specialised epilepsy surgery centre. The use of different EEG and/or imaging techniques in the pre-surgical workup will depend on the specific characteristics of each individual patient and also the expertise of the centres [49].

Despite the significant advantage of better seizure control and improved quality of life for patients with refractory epilepsy who undergo surgical treatment, the prognosis of seizure control in the long term after surgery is largely heterogeneous. In a large surgical series of patients with FCD type I, only 46% had seizure control [31]. Another surgical series of patients with type II FCD and long term follow-up showed seizure remission in 88% of patients with FCD type IIb and 74% of patients with FCD type IIa and worse outcome associated with multilobar dysplasia or incomplete resection due to the proximity of eloquent cortex [26]. It is a well-demonstrated fact that the main determinant of seizure remission after surgery in patients with FCD is the complete resection of the lesion [50,51]. Therefore, the detection of clear changes suggestive of FCD in the pre-operatory MRI and the lesion not invading the eloquent cortex are other important determinants of the surgical outcome [26,51]. A very recent large series including FCDs type I, II and III with long-term follow-up after surgery demonstrated that the seizure outcome remains stable after the first postoperative year. Also, in this series, complete resection of the epileptogenic area, lower age at surgery and unilobar localisation were indicators of long-term seizure-freedom [52].

CONCLUSION

FCD is a significant cause of epilepsy, especially amongst children who display drug resistant seizures. In recent decades, significant advances have been accomplished in expanding knowledge regarding the clinical presentation, neuroimaging findings and histological subtypes of FCD. Future studies are necessary for the better understanding of prevalence, long-term clinical prognosis and the clinical differences between the specific subtypes of FCD. Moreover, efforts must be made to recognise FCD early and treat the seizures to improve seizure control and outcomes both neuropsychological and social.

Competing interests

The authors have declared that no competing interest exists.

Author contributions

Both authors contributed equally to this work.

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