Section A -Research paper

Focal Cortical Dysplasia: Classification, Neuropathology and Diagnosis

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Article History: Received: 11.06.2023 **Revised:** 08.07.2023 **Accepted:** 15.07.2023

Abstract:

Focal cortical dysplasias are common malformations of cerebral cortical development and are highly associated with medically intractable epilepsy. They have been classified into neuropathological subtypes (type Ia, Ib, IIa, IIb, and III) based on the severity of cytoarchitectural disruption—tangential or radial dispersion, or loss of laminar structure—and the presence of unique cells types such as cytomegalic neurons or balloon cells. Most focal cortical dysplasias can be identified on neuroimaging and many require resective epilepsy surgery to cure refractory seizures. The pathogenesis of focal cortical dysplasias remains to be defined, although there is recent evidence to suggest that focal cortical dysplasias arise from de novo somatic mutations occurring during brain development. Some focal cortical dysplasia subtypes show a link to the mammalian target of rapamycin signaling cascade; this has now extended to other cortical malformations, including hemimegalencephaly.

Keywords: cortical dysplasiam sclerosis, MCD.

DOI: 10.53555/ecb/2023.12.1168

Introduction:

Focal cortical dysplasias (FCDs) comprise a spectrum of focal developmental malformations characterized by disruption of the normal cytoarchitecture of the cerebral cortex **(1).**

They are highly associated with medically intractable epilepsy. Focal cortical dysplasia and epilepsy were first associated in a report by Taylor (although previously alluded to by Crome), who reported 10 patients (adults and children) with refractory epilepsy undergoing surgical resection, who showed focal abnormalities of cortical cytoarchitecture that matched the proposed anatomical focus associated with their seizure semiology (**2).**

They hypothesized that the focal pathological changes were probably developmental and that they accounted for their seizures. The description of other focal malformations of cortical development (MCD) subtypes sharing pathological changes with FCD such as hemimegalencephaly and tuberous sclerosis complex (TSC) dates back to the 1800s. There have also been recent descriptions of new FCD syndromes, including Pretzel syndrome, autosomal dominant temporal lobe epilepsy and cortical dysplasia, and familial focal epilepsy with variable foci **(3)**.

Classification and Neuropathology:

Historically, several different FCD classification systems have been proposed, trying to link the pathological findings with developmental mechanisms, although none has consistently linked the pathology to the clinical presentation or outcome. Distinct classification schemes have been proposed to define the relevant imaging and histological features of FCD. The Palmini classification system was restructured and further subdivided FCD into type IA, IB, IIA, and IIC. The International League Against Epilepsy (ILAE) task force of the Diagnostic Methods Commission generated a new consensus classification of distinct focal cortical dysplasia subtypes based on histopathological features that yields consistent interobserver and intraobserver reliability. The ILAE classification scheme comprises a three-tiered system, including both isolated and associated FCD variants. A new and comprehensive classification scheme assumes that all MCD types result from distinct developmental and molecular genetic causes, and that these directly affect cortical development at distinct epochs and within distinct cell types **(4)**.

Table (1): New classification system of focal cortical dysplasia **(4).**

Type	Characteristic features
I	a – focal cortical dysplasia with abnormal radial cortical lamination b – focal cortical dysplasia with abnormal tangential 6-layer cortical lamination c – focal cortical dysplasia with abnormal radial and tangential cortical lamination
II	a – focal cortical dysplasia with dysmorphic neurons b – focal cortical dysplasia with dysmorphic neurons and balloon cells
III	a – architectural distortion of cortical layer in temporal lobe with hippocampal atrophy b – architectural distortion of cortical layer adjacent to glial or glioneuronal tumor c – architectural distortion of cortical layer adjacent to vascular malformation d – architectural distortion of cortical layer adjacent to other lesions acquired in early childhood such as trauma, ischemic event, encephalitis

Focal cortical dysplasia type I is characterized by abnormal cortical layering with radial microcolumns, and is of three subtypes. Focal cortical dysplasia type Ia shows radial microcolumns resembling the microcolumnar organization pattern of the early stages of cortical development; FCD type Ib shows tangential layer alterations; FCD type Ic shows a combination of both. All the three variants can show heterotopic neurons in white matter and hypertrophic neurons (outside layer 5), as well as normal neurons with abnormal dendrites. Focal cortical dysplasia type I may affect one or multiple lobes, yet preoperative magnetic resonance imaging (MRI) may be normal. Focal cortical dysplasia type I may be subtle and challenging to detect on routine neuropathology, but should be specifically sought in cases with normal preoperative MRI scans **(3)**.

Focal cortical dysplasia type II is common among epilepsy surgical series and is a major cause of antiepileptic drug-resistant epilepsy. It is more common in extratemporal areas, particularly in the frontal lobe, and is typically seen on preoperative MRI scans. Focal cortical dysplasia type IIa is characterized by dysmorphic and cytomegalic neurons, but lacking balloon cells; FCD Type IIb is characterized by dysmorphic/cytomegalic neurons *and* balloon cells. Balloon cells have an enlarged cell body and opalescent, glassy appearing, eosinophilic cytoplasm. Cortical tubers are a type of FCD found in TSC, though not included in the ILAE classification system, and occur as single or multiple lesions in more than 80% of patients with TSC. They are linked to both epilepsy and neurocognitive disabilities. Tubers are common in temporal and frontal regions and are characterized histopathologically by dyslamination, and heterogeneous cell types, such as dysmorphic neurons, reactive astrocytes, and so-called giant cells. Giant cells are histologically similar to the balloon cells found in FCD type IIb **(5)**.

Both giant cells and balloon cells express proteins characteristic of neuroglial progenitor cells, such as SOX2, nestin, vimentin, and c-myc, suggesting a failure to differentiate before migration into the cortex. The first study to examine lineage markers in FCD found that balloon cells and cytomegalic neurons expressed cell markers reflecting lineage derivation from the telencephalic ventricular zone, such as OTX-1 and MASH. A subsequent study in FCD I showed that FCD I specimens in younger patients characteristically have abnormal expression of Tbr1 and Otx1 in layer II, supporting their origins from radial glia; by contrast, FCDII showed distinct labeling of balloon cells (Pax6, ER81 and Otx1) and dysmorphic neurons (Tbr 1, N200, and Map1b), supporting their origins in intermediate progenitor cells. Tubers may be found as early as 20 weeks gestation, indicating that tubers (and by extension, focal cortical dysplasias) form during embryonic brain development, probably between weeks 10 and 20 of human gestation **(6)**.

A significant advantage of the ILAE classification was that pathological changes adjacent to or associated with substantive brain lesions (such as vascular malformations and tumors) could be defined as FCD type III. The four different subtypes of FCD type III include IIIa, associated with

hippocampal sclerosis; IIIb, associated with tumors; IIIc, associated with vascular malformations; and IIId, associated with any other lesion acquired during early life. Histopathologically, FCD type III subtypes show type I abnormalities, including altered cortical lamination. However, finding an abnormal band of small and clustered "granular" neurons in the outer part of layer II can distinguish FCDI type I from subtypes IIIa–d **(7)**.

Other types of focal MCD, such as TSC, hemimegalencephaly, and some of the newer focal cortical dysplasia syndromes have not yet been subsumed into the ILAE classification. However, cortical tubers are histologically similar to FCDIIb; hemimegalencephaly may occur both with and without balloon cells similar to FCDIIb; and familial focal epilepsy with variable features may show a "bottom-of-the-sulcus" dysplasia with a type IIa or IIb phenotype. An important corollary to these classifications is that FCDs are often heterogeneous lesions with local variations in regional cytoarchitectural abnormalities. For example, some resected lesions may contain both type I and type FCD pathologies. From a diagnostic perspective, while pathologists describe the histological variations, they tend to use the most severe FCD subtype for final diagnosis **(3)**.

Clinical Presentation:

Epilepsy, often intractable, remains the most common clinical presentation for all types of FCD as well as TSC and hemimegalencephaly. Patients usually come to clinical attention with seizures in early childhood, although seizures may start at any age. In virtually all FCD subtypes, there is close concordance between the location of the seizure onset defined by electroencephalography and the anatomic location of the FCD defined by MRI or intraoperative visualization. Furthermore, the anatomical location of FCD determines the seizure semiology. Frontal lobe epilepsy may manifest as sleep-related seizures characterized by stereotyped bilateral movements and vocalizations, sometimes with preserved consciousness. Patient with occipital lobe seizures may report visual symptoms, such as seeing dots or shapes in different colors. Regardless of semiology, recalcitrant and poorly controlled seizures contribute to cognitive impairment in children and adults. Other clinical presentations include developmental delay, behavioral issues, autism spectrum disorders, and sometimes focal neurologic deficits, depending on the size and location of the cortical lesion. The surgical outcome may vary with the pathological FCD subtype **(8)**.

Radiographic Findings:

With greater availability of more advanced neuroimaging in the 1990s, specifically brain MRI, it became apparent that focal MCDs are more common in patients with intractable epilepsy than previously thought. Newer imaging shows MCD to be radiographically heterogeneous, with distinct signal characteristics, extent, and location. However, focal malformations of cortical development sometimes do not show on imaging, and can be found only on histopathological examination of resected tissue specimens. Nevertheless, neuroimaging is central to identifying and

diagnosing FCDs. Common findings on brain MRI include increased cortical thickness, subtle changes in the smoothness of gyri or sulci, and changes in subcortical white matter signal. Typically, FCDs do not enhance with gadolinium, although approximately 5% of tubers in TSC enhance very slightly. In terms of radiographic–pathologic correlation, FCD type I appears as mild hyperintensity of the white matter in T2/fluid-attenuated inversion-recovery (FLAIR) sequences with loss of gray/white matter differentiation **(9)**.

On the other hand, MRI findings in FCD type IIb (dysmorphic neurons with balloon cells) include thickening of the cortex with loss of gray/white matter differentiation as well as a "transmantle sign"–tapering of abnormal white matter signal from the FCD in the cortex to the ventricular surface. About 40% of patients with FCD type I and approximately 10% in type II have a normal brain MRI. Thus, a normal brain MRI in a patient with intractable epilepsy does not rule out FCD. Magnetic resonance imaging findings favoring FCD rather than a tumor include cortical gray matter thickening and a transmantle sign. Tubers are not static lesions and there may be dynamic changes over time including calcification and cystic degeneration. The evolution of cystic changes is associated with a *TSC2* gene mutation and with having more severe seizures. More recently, three tuber types (A, B, C) have been distinguished from their MRI features **(10)**.

However, there is as yet no histopathological classification scheme for tubers; this will represent an important advance in understanding of epileptogenesis in TSC patients. In addition to MRI, functional imaging such as fluorodeoxyglucose-positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) can help, particularly in epilepsy localization before surgery. Focal cortical dysplasias typically show focal regional hypometabolism on FDG-PET imaging even in MRI-negative cases. Ictal SPECT detects enhanced cerebral blood flow during the seizures, confirmed with video-electroencephalogram (EEG) monitoring, and helps with localization in almost half of the patients with FCD. The sensitivity of FDG-PET scan in detecting FCD is 69 to 98%, and for ictal-SPECT it is 48 to 64% **(11)**.

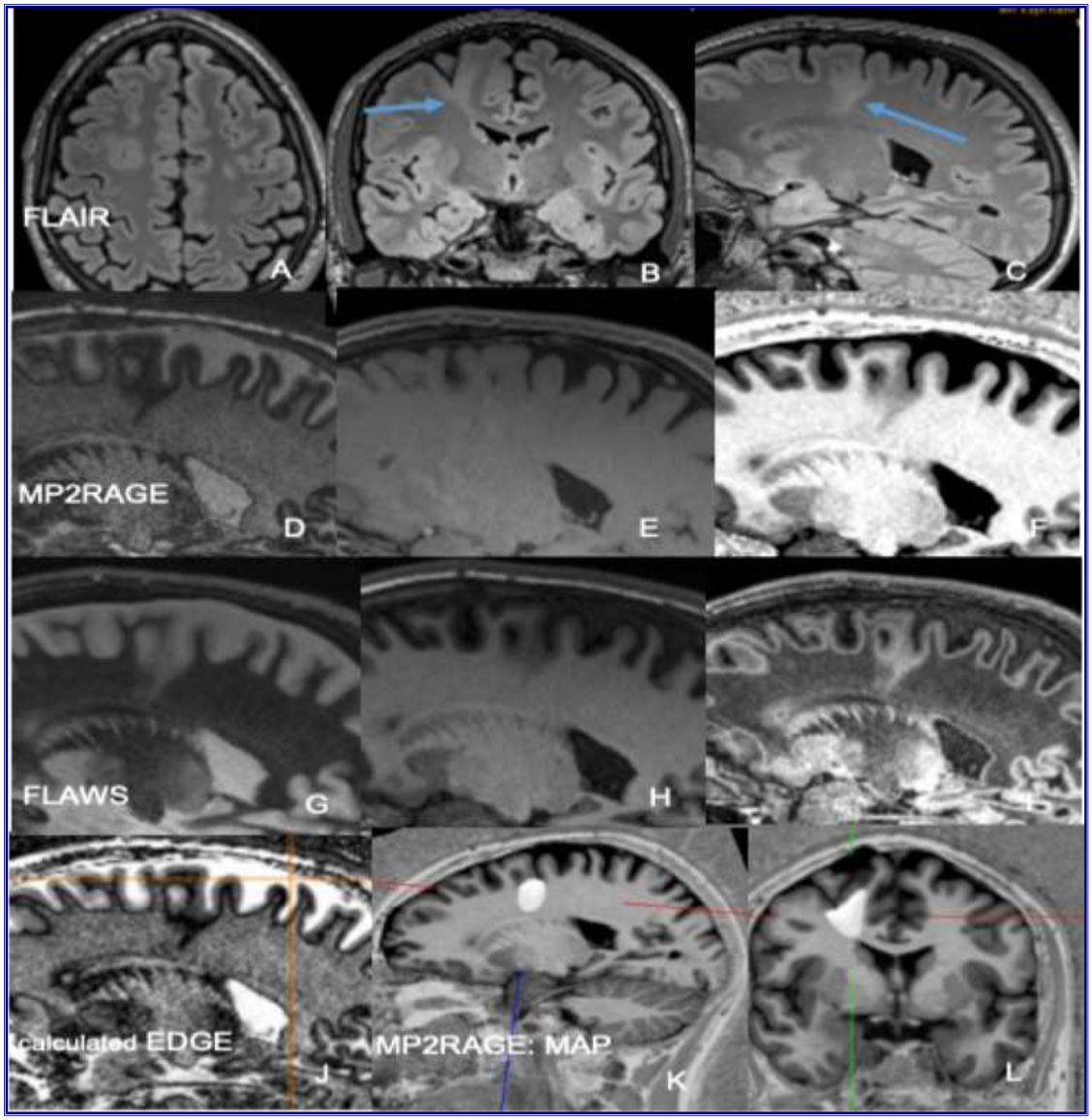

Figure (1): FCD type IIb in the depth of the right superior frontal sulcus. **A**–**C** 3 Tesla axial, coronal, and sagittal 3D FLAIR SPACE images show a thickenend cortex and a hyperintense transmantle sign tapering towards the frontal horn of lateral ventricle (**B**, **C**: arrow). **D**–**F** 3 Tesla sagittal MP2RAGE images at inversion times TI of 700 ms (**D**) and 2500 ms (**E**). Calculated so-called unified image (**F**). **G**–**I** 3 Tesla sagittal FLAWS images at inversion times TI of 409 ms (**G**) and 1160 ms (**H**). Calculated minimum intensity image (**I**). **J** 3 Tesla calculated sagittal EDGE image at an inversion time of 442 ms according to Bydder and Young (1995) and Hornak (2008). **K**–**L** MAP-postprocessed MP2RAGE images after inverse normalization and co-registration of the CNN output map to the unified images **(12).**

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