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Brain Pathology

MINI-SYMPOSIUM

Focal cortical dysplasia type 1

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Abstract

The ILAE classification of Focal Cortical Dysplasia (FCD) from 2011 has quickly gained acceptance in clinical practice and research and is now widely used around the world. This histopathology-based classification scheme proposed three subtypes, that is, FCD Type 1 (with architectural abnormalities of the neocortex), FCD Type 2 (with cytoarchitectural abnormalities of the neocortex) and FCD Type 3 (architectural abnormalities of the neocortex associated with another principle lesion acquired during early life). Valuable knowledge was gathered during the last decade validating the clinical, pathological and genetic classification of FCD Type 2. This is in contrast to FCD subtype 1 and 3 with only few robust or new insights. Herein, we provide an overview about current knowledge about FCD Type 1 and its three subtypes. Available data strengthened, however, FCD Type 1A in particular, whereas a comprehensive clinico-pathological specification for FCD Type 1B and 1C subtypes remain to be shown. The lack of a valid animal model for FCD Type 1 further supports our call and the ongoing need for systematic research studies based on a careful clinico-pathological and genetic stratification of patients and human brain tissues.

KEYWORD
focal cortical dysplasia type 1,

1 | INTRODUCTION

In 2011 an ad hoc Task Force of the ILAE Diagnostic Methods Commission released a proposal for the classification of "The clinico-pathological spectrum of Focal Cortical Dysplasias" (1). This classification scheme has quickly gained acceptance and is now widely used. A multicentre study reporting histopathological diagnoses from brain specimen in over 9000 surgically treated epilepsy patients, conclusively showed that FCD was the most frequent diagnosis amongst children and young adults (2). Based on microscopically visible abnormalities of the neocortical architecture, the ILAE classification proposed three subtypes of Focal Cortical Dysplasia Type 1 (FCD 1), i.e. FCD 1A with an abnormal radial organization, FCD 1B with abnormal tangential layering and FCD 1C with both abnormal radial and tangential architecture. This classification scheme was anticipative and the need for re-evaluation for feasibility in clinical and neuropathological practice was emphasized. Focal Cortical Dysplasia Type 1 did not and still does not fulfil the same well-documented and indisputable diagnostic criteria as does FCD 2 in terms of clinical phenotype, neuroimaging, genetics and neuropathological findings. However, surgical therapy is a promising option in these patients (3). The number of published works on FCD 1 has increased in the past decade but is far fewer than those addressing FCD 2,

sustaining that FCD 1 is still a field of diagnostic uncertainties and controversies. This is highlighted by major differences reported between epilepsy centres regarding the incidence of FCD 1, in clinical terms and considerable discrepancies in clinical presentations as well as of referred histological FCD 1 subtypes. These gaps are most likely not explicable by patient selection bias between centres and are also seen when comparing strictly paediatric or adult series. The subtypes of FCD 1 proposed in the ILAE Neuropathological Classification of 2011 (1) are now challenged, with FCD 1A persisting as the only credible subtype; FCD 1B and 1C probably do not really exist or represent other types of lesions such as associated architectural disturbances to perinatal ischaemic encephalopathy or toxic encephalopathies (4). Nevertheless, FCD 1A remains as a frequent finding in paediatric age onset of focal epilepsy and requires more intense investigation to disclose the missing data for its criteria to approach those of FCD 2 and for genetic aetiological correlation. The same applies for FCD 3, which is usually associated with another primary lesion (FCD 3A with hippocampal sclerosis, FCD 3B with epilepsy associated tumours, FCD 3C with vascular malformations and FCD 3D with epileptogenic lesions acquired in early life) and also needs more precise definition and explanation.

2 | CLINICAL PHENOTYPE OF FOCAL CORTICAL DYSPLASIA TYPE 1

2.1 | Presentation

The presenting symptom of FCD 1 is onset of focal epilepsy in infancy or early childhood, with localization usually in the posterior half of the cerebral cortex: parietal, posterior temporal and occipital lobes (5–9). Gender predominance is not evident, nor are there racial or ethnic predilections. Animal models of FCD 1 have not yet been discovered or created. The epilepsy often becomes intractable and resistant to anti-seizure medications. Developmental delay is common in these paediatric patients.

2.2 | Neuroimaging findings

Magnetic resonance imaging (MRI) often reveals blurring of the grey/white matter junction (5, 9, 10). This finding may be correlated with an excessive number of heterotopic neurons in the U-fibre layer which form local synaptic plexi that also become integrated into the synaptic circuitry of the overlying cortical epileptic networks (11). However, intense signalling such as seen in FCD 2 is not demonstrated, though subtle increases in T2-weighted and FLAIR sequences may be observed (5, 9, 10). The abnormal arrangement of cortical neurons does not change the cellular density of the cerebral tissue or its vascular perfusion. The transmantle sign dysplasias frequently seen by MRI in FCD 2 do not occur in FCD 1. At times no lesions are visualized by MRI at the EEG paroxysmal focus in FCD 1 (i.e. "non-lesional"). It is for this reason that some neuroradiologists and neurologists question its very existence because they cannot recognize the epileptogenic focus as one can do with FCD 2. However, functional imaging studies such as positron emission tomography (PET) may show focal alterations in cerebral metabolism (10). Also, none of the present generation of neuroimaging techniques is capable of demonstrating alterations at a microscopic level, though higher Tesla equipment does provide greater macroscopic resolution.

2.3 | Electrophysiological findings

Electroencephalography (EEG) and intraoperative electrocorticography (ECoG) including in-depth electrodes are useful in localizing the epileptogenic focus but the type of paroxysmal activity is not distinctive enough to differentiate FCD 1 from other cortical lesions resulting in focal epilepsy (5, 8, 9). Because the lesion often is extensive or even multilobar, localization of the focus by EEG may be difficult (9).

2.4 | Prognosis

Despite the fact that the histopathological pattern of FCD 1 is not nearly as severely dysplastic as in FCD 2, the prognosis is not as good as in FCD 2. The reasons are not only the intractability of FCD 1 to medical treatment of the seizures, but even with surgical resection outcome is not as good. The wide extent of the lesion renders it difficult for the neurosurgeon to identify margins to resect without encroaching on "eloquent" cortex and white matter that may leave severe neurological deficits in motor function, vision, language and cognition (5, 8, 9). Many children with FCD 1 have intellectual deficits, learning disabilities and maladaptive behaviours in later childhood (9). Many also continue to have seizures postoperatively with variable responses to medical treatment.

2.5 | Genetics

No specific genetic mutation has been demonstrated to date in FCD 1, unlike the abundance of genetic data demonstrated in FCD 2. None of the genes of the mTOR signalling pathway, including the related PIK3C, AKT and GATOR families are defective or deficient in FCD 1 as they are in FCD 2. However, a few families are now identified in whom siblings have FCD 1, suggesting a

Mendelian autosomal transmission (12). Furthermore, as mentioned earlier, generalized micro-columnar architecture occurs in some metabolic/genetic diseases (13). Cases of FCD 1 have not been studied genetically as much as FCD 2 and it is likely that genes will be discovered in future to better establish its aetiology. However, DNA methylation analyses can distinguish FCD 1A from other FCD variants (14) (Holthausen et al., manuscript submitted for peer review).

3 | NEUROPATHOLOGICAL PHENOTYPE OF FOCAL CORTICAL DYSPLASIA SUBTYPE IA

The characteristic vertical dyslamination with micro-columns of neurons that are the most prominent microscopic feature of FCD 1A (Figure 1) (4, 5, 15) are not yet quantitated in terms of how many micro-columns are required in a high-power field to be regarded as pathological and whether regional differences exist between gyri and lobes of cortex. Scattered micro-columns occur in the cerebral cortex of all normal mature brains, especially where gyri curve at the gyral crowns and in the depths of sulci. They are particularly frequent in temporal neocortex, especially the temporal pole (13, 15–18). There is no consensus amongst neuropathologists so far regarding the quantitation of how many micro-columns within a 200X microscopic field are too many to be considered abnormal, though attempts have been made (19). Regional differences in normal mature neocortical cytoarchitecture already are known qualitatively and were classified as early as 1908 by Brodmann (20); layer 5 normally predominates in frontal lobe and layer 4 in occipital lobe, for example.

Micro-columnar architecture is the dominant histological pattern in the normally developing human foetal cortical plate throughout the first half of gestation, horizonal lamination superimposed beginning about 22 weeks gestation (21). The transcription product of the *Reelin* (*RELN*) gene produced by Cajal-Retzius neurons in the molecular zone is essential to the organization of the early cortical plate and its columnar architecture (22–26). Cortical lamination often is severely altered in polymicrogyria and Cajal-Retzius neurons are clustered as part of the neuropathology of this disorder (27–29). These Cajal-Retzius neurons appear before the first wave of radial neuroblast migration from the subventricular zone to the cortical plate and are prominent throughout foetal life (30). These unique neurons were thought to disappear with maturation of the cortex, but are now known to persist into adult life though they become sparse with growth of the cortex and perhaps still might play a role in regeneration after cortical injury (31, 32). The subplate zone also contains GABAergic Reelin-secreting neurons essential to cortical plate organization; this zone is transitory and disappears in late foetal life (25, 30–32). Yet another factor important in cortical architectural organization are extracellular matrix dis-adhesion molecules that detach migratory neuroblasts from their radial glial fibre when they reach the cortical plate so that neuroblasts behind can bypass to reach the cortical surface for the inside-out arrangement of the earliest arrivals forming the deepest layers (23, 29).

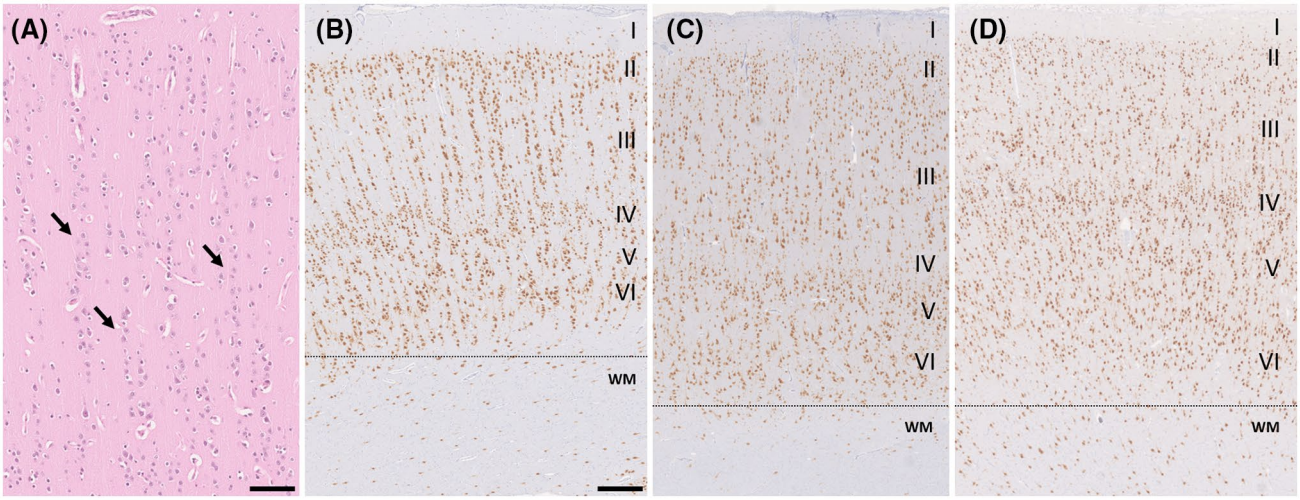

FIGURE 1 Focal cortical dysplasia type 1A (FCD 1A) in a five-year-old girl with right hemispheric epilepsy. (A) Microcolumnar arrangement of neurons is already suggested on haematoxylin & eosin staining (HE) (arrows). (B) NeuN shows neuronal columnar arrangement in the specimen obtained from the occipital lobe (see also comparison to regular six-layering in an area not affected by this architectural disturbance in C). In addition, moderate blurring of the grey-white matter boundaries (dotted line). (C) Normal appearing cortical ribbon with regular six-layering and sharp grey white matter junction (dotted line) (NeuN immunohistochemistry). (D) NeuN staining of the same patient (shown in A & B) in a specimen obtained from the temporal lobe does not show evidence for a microcolumnar arrangement but severely blurred grey-white matter boundaries (dotted line). I–VI: Cortical layers. WM, white matter. Scale bar in A: 100 μm. Scale bar in B: 250 μm, applies also for C & D.

In FCD 1A, radial columns of synaptophysin reactivity alternates between micro-columns of neurons; in normal developing brain the appearance of synaptophysin reactivity in the cortex appears with horizontal lamination, earliest in the molecular zone followed by deep cortical layers and finally superficial laminae (21). This pattern is not seen in the first half of gestation when physiological micro-columns predominate because there are no intrinsic synapses or synaptophysin reactivity in the cortical plate until the second half of gestation (33). Radial synaptic columns occur in normal brain but are exceeded by intercolumnar connections that occur with superimposed mature horizontal lamination (13). An extracellular proteoglycan, keratan sulphate, normally binds to neuronal membranes except for dendritic spines and repels glutamatergic axons while facilitating GABAergic axons. This explains why axosomatic synapses are inhibitory and axodendritic synapses are excitatory. The distribution of KS normally follows a horizontal laminar pattern in normally developing brains but in FCD 1A it is less regular and forms irregular radial columns (34).

Another piece of neuropathological evidence that FCD 1A is an epileptogenic structural lesion is that in the U-fibre layer beneath the region of cortex containing FCD contains an excessive number of heterotopic neurons. These displaced neurons form complex synaptic plexi within the U-fibre layer, some axons of which ascend into the cortex to be integrated into synaptic networks (11). Whether U-fibre layer plexi can initiate seizures is uncertain, but they may contribute to cortical epileptic activity and its propagation.

Glial cells in both white and grey matter, including satellite glial cells, at foci of FCD 1 (and also FCD 2) exhibit upregulation of the heat-shock chaperone protein α-B-crystallin, that serves as a non-specific marker of epileptic foci generally but also suggests a structural lesion at the site of the focus (35). Astrogliosis in both grey and white matter is variable in individual cases.

4 | NEUROPATHOLOGICAL PHENOTYPE OF FOCAL CORTICAL DYSPLASIA SUBTYPES 1B AND 1C

As already noted, there is considerable doubt whether FCD 1B and 1C are valid clinic-neuropathological entities are developmental malformations (4). Lamina-specific immunocytochemical and genetic markers for synaptic connections are documented (36–39) and horizontal lamination is the predominant mature histological pattern of cerebral neocortex. Nevertheless, many FCD described as subtype 1B are actually secondary to perinatal ischaemic encephalopathy with selective loss of cortical neurons of a particular type of specific laminae (40, 41), and should be classified as associated FCD type 3D. The same applies also for FCD type 1C. They might play a supplementary role, but are not likely the primary factor in pathogenesis.

5 | DISCUSSION

In 2011, an ad hoc Task Force of the ILAE Diagnostic Methods Commission released a proposal for the classification of Focal Cortical Dysplasia (1). This three-tiered classification scheme proposed criteria for dividing the group of the former Palmini Type 1 FCDs into FCD subtypes 1 and 3, depending whether the dyslamination is associated to a distinct principal lesion (FCD types 3) or remains isolated (FCD types 1). The histopathological hallmark of FCD 1A is an abnormal radial cortical layering with microcolumnar organization of the cortical ribbon, FCD 1B with abnormal tangential layering with horizontal dyslamination and FCD 1C with both abnormal radial and tangential layering. In the context of FCD type 1, one major challenge in the histopathological work-up of specimen obtained from epilepsy surgery is the evaluation of architectural/cortical layering disturbances because cellular or cytoarchitectural abnormalities are missing. The level of experience of reporting (neuro)pathologists together with so far little knowledge about distinct clinic-pathological phenotypes or syndromes may lead to most of all overestimation of this type of FCD. The histopathology in surgical resections of the focus cannot be ignored or dismissed as a variant of normal, as all epileptic foci have underlying structural lesions. At times they may be difficult to demonstrate histologically, may be subcellular and require ultrastructural examination of organelles, or they may be membrane lesions of ion channels or neurotransmitter receptors, but one must endeavour to demonstrate a structural defect and not accept the terms "idiopathic" or "non-lesional" if no abnormality can be demonstrated by neuroimaging or by H&E histological examination alone. In the case of FCD 1A, the characteristic microcolumns require better definition with microscopic semi-quantitation of straight uncurved parts of the gyrus along its lateral surface facing a sulcus, with separate criteria for different cortical regions.

It has been proposed that FCD 1 might be a maturational arrest of a physiological state of the cortical plate in the first half of gestation as one mechanism of pathogenesis, though not necessarily the only factor (13). Micro-columnar architecture of FCD 1A is seen not only in FCD 1, but also in a more generalized distribution throughout all lobes of the cerebral cortex as a developmental maturational arrest in some inborn metabolic and genetic diseases, including DiGeorge syndrome (22q11.2 deletion) and methylmalonic acidaemia, an organic aciduria (21), together with other aspects of maturational delay such as myelination. Cortex adjacent to a porencephalic cyst resulting from middle cerebral artery occlusion at mid-gestation also

exhibits foetal micro-columnar architecture, probably as maturational arrest secondary to chronic ischaemia (15, 21).

Significant efforts have been made to better delimit the FCD Type 1 subgroup from other entities of this difficult to diagnose spectrum, including mild malformations of cortical development (mMCDs) and non-lesional cases with microscopically proven gliosis only. By reevaluation of retrieved histopathological exams and clinical reports, a new clinico-pathological entity with overlapping clinical findings to the FCD 1 group has been identified (42, 43). It has been termed "Mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE)" and represents a major differential diagnosis to FCD Type 1. Both lead to childhood-onset, drug-resistant epilepsy and share localized increased signals on T2 weighted images and FLAIR, if MRI-positive. However, recent studies strongly argue for distinct molecular fingerprints of FCD 1A and MOGHE, with DNA methylation classes as well as brain somatic mutations of the SLC35A2 gene as most significant denominator (14, 44).

In conclusion, FCD 1A is a malformation of cortical development, lamination and maturation and results of DNA methylation analyses able to distinguish FCD 1A from other FCD variants (14) (Dr. Hans Holthausen, personal communication, February 2021) further emphasize a specific clinico-pathological entity. The hypothetically proposed FCD subtypes 1B and 1C, by contrast, probably do not exist as isolated true developmental malformations but rather are acquired lesions associated with hypoxia/ischaemia, congenital infections or other perinatal insults affecting the brain and should be classified into the group of associated FCD type 3. Wang and co-workers show evidence for this scenary (41). In contrast, robust confirmation for particular FCD 1B and 1C clinico-pathological phenotypes or syndromes have not been described so far and further scientific studies are essential for the proof of their true existence.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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