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Challenges in managing epilepsy associated with focal cortical dysplasia in children

Lily C. Wong-Kisiel[a,1], Thomas Blauwblomme[b,1], Mai-Lan Ho[c], Nathalie Boddaert[d], Joseph Parisi[e], Elaine Wirrell[a], Rima Nabbout[f,g,*]

[a] Department of Neurology, Mayo Clinic, 200 First St., SW, Rochester, MN, 55905, USA
[b] Department of Pediatric Neurosurgery, Hôpital Necker, Assistance Publique Hôpitaux de Paris, Université Paris Descartes, Sorbonne Paris Cité, 149 rue de Sevres, 75015, Paris, France
[c] Department of Radiology, Mayo Clinic,200 First St., SW, Rochester, MN, 55905, USA
[d] Department of Pediatric Radiology, Hôpital Necker, Assistance Publique Hôpitaux de Paris, Université Paris Descartes, Sorbonne Paris Cité, 149 rue de Sevres, 75015, Paris, France
[e] Department of Laboratory Medicine and Pathology, Mayo Clinic, 200 First St., SW, Rochester, MN, USA
[f] Centre for Rare Epilepsies, Department of Pediatric Neurology, Necker Hospital, Assistance Publique – Hôpitaux de Paris, Université Paris Descartes, Sorbonne Paris Cité, 149 rue de Sevres, 75015, Paris, France
[g] INSERM U1129, Paris Descartes University, CEA, Gif sur Yvette, France

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ABSTRACT

Focal cortical dysplasia (FCD) is the most common cause of intractable focal epilepsy in children, in whom seizures are most commonly pharmacoresistant from onset. This review summarizes the current understandings of the epidemiology, natural history, and the proposed mechanisms of epileptogenisis in FCD. Advances in neuroimaging techniques have enhanced the recognition of this pathology, which can be subtle. Illustrative neurophysiology and imaging examples are provided to help the clinicians identify diagnostic evidence of suspected FCD. Given the refractory course to pharmacologic management, alternative options such as ketogenic diet, resective surgery or neuromodulation can be considered. Recognition of FCD pathology in children with early onset epilepsy should prompt timely evaluations for resective surgery, which may render a significant number of patients seizure-free and improve neurocognitive outcome.

1. Introduction

Focal cortical dysplasia (FCD) is the most common cause of intractable focal epilepsy in children (Bast et al., 2006; Luders and Schuele, 2006). This pathology, first described by Taylor et al. in 1971 (Taylor et al., 1971), is characterized by dyslamination, ectopic neurons in white matter and abnormal cytomegalic neurons and balloon cells. Many affected children can benefit from surgical resection, with both improved seizure and neurocognitive outcome. Recognition of this pathology has been markedly enhanced by significant advances in neuroimaging techniques.

2. Etiology of FCD

In most cases, FCD is believed to arise from abnormal brain development in utero, due to both intrinsic genetic as well as extrinsic environmental factors that disrupt normal cortical development (Barkovich et al., 2012), which may include perinatal and postnatal injury (Krsek et al., 2010; Marin-Padilla, 1999; Sutula, 1998), as well as viral infection (Chen et al., 2012). In support of an environmental etiology, mTOR activation has been linked to maternal fetal infection with HPV16. In a study of 50 human brain specimens of FCD type II, immunostaining displayed the oncoprotein E6, and PCR studies found HPV16 DNA and RNA (Chen et al., 2012; Liu et al., 2014). However, two further studies could not replicate these results, as viral DNA was not found in brain samples from 28 FCD patients, and immunohistochemistry for HPV proved to be non-specific (Coras et al., 2015; Shapiro et al., 2015). In support of a genetic etiology, DEPDC5 mutations were found in 3 Australian families who suffered from both focal non-lesional epilepsy and FCD (Scheffer et al., 2014). In another

* Corresponding author at: Centre de Référence épilepsies Rares (CReER), Service de Neurologie Pédiatrique, Hôpital Necker-Enfants Malades, Université Paris Descartes, 149 rue de Sèvres, 75015 Paris, France.
E-mail addresses: wongkisiel.lily@mayo.edu (L.C. Wong-Kisiel), thomas.blauwblomme@aphp.fr (T. Blauwblomme), mai-lan.ho@mayo.edu (M.-L. Ho), nathalie.boddaert@aphp.fr (N. Boddaert), parisi.joseph@mayo.edu (J. Parisi), wirrell.elaine@mayo.edu (E. Wirrell), rima.nabbout@aphp.fr (R. Nabbout).
[1] Co-first authors.

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Table 1
International League Against Epilepsy classification of focal cortical dysplasia.

FCD type I	Ia = abnormal radial cortical lamination	Ib = abnormal tangential cortical lamination	Ic = abnormal radial and tangential cortical lamination	
FCD type II	IIa = dysmorphic neurons		IIb = dysmorphic neurons and balloon cells	
FCD type III	IIIa = temporal cortical lamination abnormalities associated with hippocampal sclerosis	IIIb = cortical lamination abnormalities adjacent to glial or glioneuronal tumor	IIIc = cortical lamination abnormalities adjacent to vascular malformation	IIId = cortical lamination abnormalities adjacent to early encephaloclastic injury (trauma, ischemia, encephalitis)

study, whole exome sequencing from 4 patients with FCD found 3 variants in the mTOR gene associated with FCD type IIb, and 15.6% of their surgical specimens of FCD had mTOR mutations. Moreover in utero electroporation of mutation p.Leu2427Pro in mice has been demonstrated to cause seizures, and histological abnormalities comparable to human FCD (Lim et al., 2015).

3. Classification of FCD

FCD refers to a spectrum of cortical malformations resulting from disruptions in migration (Barkovich et al., 2012; Barkovich et al., 2005; Guerrini et al., 2008; Kuzniecky, 2006; Palmini et al., 2004; Spreafico and Blumcke, 2010). The 2010 classification of the International League Against Epilepsy (ILAE) subdivides FCD into three types based on histopathologic findings (Table 1) (Blumcke et al., 2011). FCD type I refers to disruptions of radial cortical lamination (Ia), tangential cortical lamination (Ib), or both (Ic). FCD type II, or Taylor type dysplasia, refers to a localized abnormality with dysmorphic neurons, without (IIa) or with (IIb) the presence of balloon cells, progenitor-like cells with high epileptogenic potential (Fig. 1). FCD type III refers to "dual" or concurrent pathology, in which dysplasia occurs in conjunction with a distinct pathologic abnormality. This can include admixed temporal lobe dysplasia and hippocampal sclerosis (IIIa), glial or glioneuronal tumors (IIIb), vascular malformations (IIIc), or encephaloclastic insult such as ischemia, infection, or trauma (IIId). Many additional dysplasias have been described, including sublobar dysplasia; complex dysplasias with associated polymicrogyria or gray matter heterotopia; and multifocal, segmental, or diffuse migrational abnormalities.

4. Frequency of FCDs

The exact incidence of FCD in children with epilepsy is unknown, as reported studies are biased by patient selection.

4.1. Based on imaging studies of children with epilepsy

The International League Against Epilepsy has published guidelines for imaging of children with recent-onset epilepsy (Gaillard et al., 2009). Although thinner slices or three-dimensional volume acquisition studies using specific epilepsy protocols will be highest yield, a negative MRI still does not definitively exclude FCD. Furthermore, MRI technology has evolved markedly in the last 5–10 years, and studies performed prior to this time may have suboptimal rates of lesion detection. Additionally, many imaging studies report on rates of all malformations of cortical development, but do not specifically parse out FCDs.

In studies evaluating all children with new onset epilepsy who undergo MRI imaging, cortical malformations, including tuberous sclerosis complex (TSC) have been reported in 1.8–2.4% of cases (Berg et al., 2000; Dhamija et al., 2011; Doescher et al., 2006). Studies limited to infantile-onset seizures (1–24 months of age) show higher rates, with 16–21% having malformations of cortical development, of which 17%–36% are FCDs or TSC (Eltze et al., 2013; Hsieh et al., 2010). In new-onset West syndrome, malformations of cortical development were found in 16–23% of cases, with 7.7% being due to either FCD or TSC (Osborne et al., 2010; Wirrell et al., 2015). Finally, population-based studies of non-syndromic focal-onset or new-onset temporal lobe epilepsy in children showed that MRI reveals cortical malformations including tuberous sclerosis in 1.7–9.3% of cases (Harvey et al., 1997; Wirrell et al., 2014).

4.2. Based on surgical pathology from epilepsy surgery cases

Large surgical series of adults and children undergoing resective surgery for pharmacoresistent focal epilepsy have shown that approximately 23% have FCD on pathology (Fauser et al., 2006; Tassi et al., 2002). On resected brain specimens from 9523 patients who underwent epilepsy surgery for drug-resistant seizures over 25 years, Blumcke et al. showed that hippocampal sclerosis was the most common histopathological diagnosis among adults and focal cortical dysplasia was the most common diagnosis among children (Blumcke et al., 2017). Series solely focused on pediatric patients show similar, albeit slightly higher rates of 25–29% (Bartolini et al., 2017; Mrelashvili et al., 2015). Rates appear even higher if cases are limited to very young children − 38–76% of cases operated on prior to 3 years of age are found to have FCD (Duchowny et al., 1998; Dunkley et al., 2011; Kumar et al., 2015; Steinbok et al., 2009; Sugimoto et al., 1999; Wyllie et al., 1996). In a single study limited to children with drug resistant temporal lobe epilepsy with hippocampal sclerosis on MRI, 47% had associated FCD (Muhlebner et al., 2016).

5. Natural history of epilepsy associated with FCD

The majority of epilepsies associated with FCD have their onset early in life. In a study of 120 cases of FCD in children and adults, 61% had epilepsy onset before 5 years and 92.5% before 16 years of age (Fauser et al., 2006). In another study of 28 infants with FCD who had seizure onset before 12 months of age, half started having seizures in the first month of life (Lortie et al., 2002). Studies have not found a consistent correlation between age at epilepsy onset and localization, with similar ages of onset with temporal, extratemporal and multilobar FCD (Fauser et al., 2006; Lortie et al., 2002). However FCD with cytoarchitectural abnormalities, including giant neurons and balloon cells (FCD types IIa and IIb), are associated with earlier age of seizure onset than those with architectural abnormalities alone (FCD type Ia) (Fauser et al., 2006; Widdess-Walsh et al., 2005). Furthermore one study suggested that FCD type IIa is associated with a more severe phenotype, with higher rates of neonatal onset, hemiparesis and severe cognitive impairment compared to FCD type IIb (Lawson et al., 2005).

There is evidence that subtypes of FCD differ based on localization with FCD type I being more commonly found in temporal lobe epilepsy and FCD type 2 in extratemporal cases (Bartolini et al., 2017; Tassi et al., 2002).

While many children with FCD present with intractable focal epilepsy, such localized brain lesions can also result in generalized EEG abnormalities, generalized seizures and epileptic encephalopathy. In very young infants, Lortie reported that initial seizures are typically focal and often very frequent (Lortie et al., 2002). Semiology is determined by topography of the FCD, with posterior lesions resulting in ocular movements, nystagmus and ocular flutter, central lesions resulting in focal clonic activity and frontal lesions leading to tonic posturing (Lortie et al., 2002). Conversely, Fauser reported that generalized semiology was commonly seen at seizure onset, with generalized