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Widespread frontal lobe cortical dysplasia or partial hemimegalencephaly: a continuum of the spectrum

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ABSTRACT – Focal cortical dysplasia (FCD) type II and hemimegalencephaly (HME) are currently considered as a continuum of pathology, the most important distinction being the extent or the size/volume of the lesion. While partial HME involving the posterior cortex has been well described, we present an unusual case with a dysplastic lesion of the whole frontal lobe. A 17-year-old boy had focal seizures from the age of nine years. Apart from diminished right-hand dexterity, his neurological and cognitive status were unremarkable. The course of his epilepsy exhibited a relapsing-remitting pattern, with prolonged periods of remission. Imaging showed dysplastic left frontal lobe (including paracentral lobule) thickened cortex with an abnormal gyration pattern resembling polymicrogyria, as well as dystrophic calcifications and hypodensity scattered throughout the white matter. This patient represents an intermediate case within the FCD type II/HME spectrum. Localization of the lesion in the frontal lobe as well as clinical characteristics (childhood onset, relapsing-remitting epilepsy, without hemiparesis and overt cognitive impairment) are more consistent with FCD type II, while a range of MRI features is shared between HME and FCD type II.

Key words: cortical dysplasia, partial hemimegalencephaly, frontal lobe, epilepsy

Hemimegalencephaly (HME) is a rare malformation of cortical development characterized by hamartomatous overgrowth of one cerebral hemisphere and is associated with developmental delay, contralateral hemiparesis, and severe epilepsy, typically developing within the first few months of life (Flores-Sarnat, 2002). Focal cortical dysplasia (FCD) type II refers to a localized malformation, characterized by disrupted cortical lamination and cytological abnormalities (dysmorphic neurons with balloon cells in type IIb or without in type IIa) (Blümcke *et al*., 2011). Epilepsy associated with FCD appears at any age, mostly in childhood, and usually is drug resistant

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(Fauser *et al.*, 2006) but not accompanied by significant neurological deficits. Microscopically, sections of the cortex in FCD IIb and HME are generally indistinguishable, both showing similar findings of dysplastic megalocytic neurons, balloon cells, dyslaminated cortical architecture, and abnormal glial cells, mixed with neurons and glia that appear histologically normal (Najm *et al.*, 2018). Recent studies provide evidence that HME and FCD type IIb are caused by mutations in the same mTOR pathway genes; the most important distinction between the two is their relative extent or the size/volume of the lesion, which reflect the progenitor cell and developmental time when the mutation occurred (Sarnat and Flores-Sarnat, 2014; D'Gama *et al.*, 2017). Partial HME characteristically involves the posterior quadrant (D'Agostino *et al.*, 2004) and only three cases of limited frontal lobe malformation have been reported so far (Ono *et al.*, 2016).

We describe a patient with malformation involving the entire frontal lobe, whose clinical and radiological characteristics illustrate the continuum of the spectrum of HME and FCD.

Case study

A 17-year-old, left-handed boy experienced his first seizure at the age of nine years. He was born at term by uncomplicated delivery to healthy non-consanguineous parents with normal antenatal history. Family history was unremarkable. General physical and neurological examination were normal and he did not have impairment of gross motor skills, but his right arm dexterity was slightly diminished. The patient's intelligence was not formally evaluated, however, he was able to attend high school and expected to graduate the following year. The seizures were characterized by eye deviation to the right, bilateral eye blinking, and right arm and leg clonic movements. The EEG showed continuous slow activity over the left frontal region and epileptiform discharges with the maximum over F3/C3 electrodes.

MRI showed dysplastic left frontal lobe (including paracentral lobule) separated from the rest of the brain by a deep postcentral sulcus on the lateral surface and marginal sulcus on the medial surface (*figure 1*). The cerebral cortex was thickened with blurring of the grey-white matter junction and abnormal gyration pattern resembling polymicrogyria. The frontal lobe and ipsilateral ventricle were moderately enlarged and there was slight midline shift. Dystrophic calcifications and hypodensity were scattered throughout the white matter. The course of his epilepsy exhibited a relapsing-remitting pattern; early seizure remission of one year (on oxcarbazepine) followed by seizure

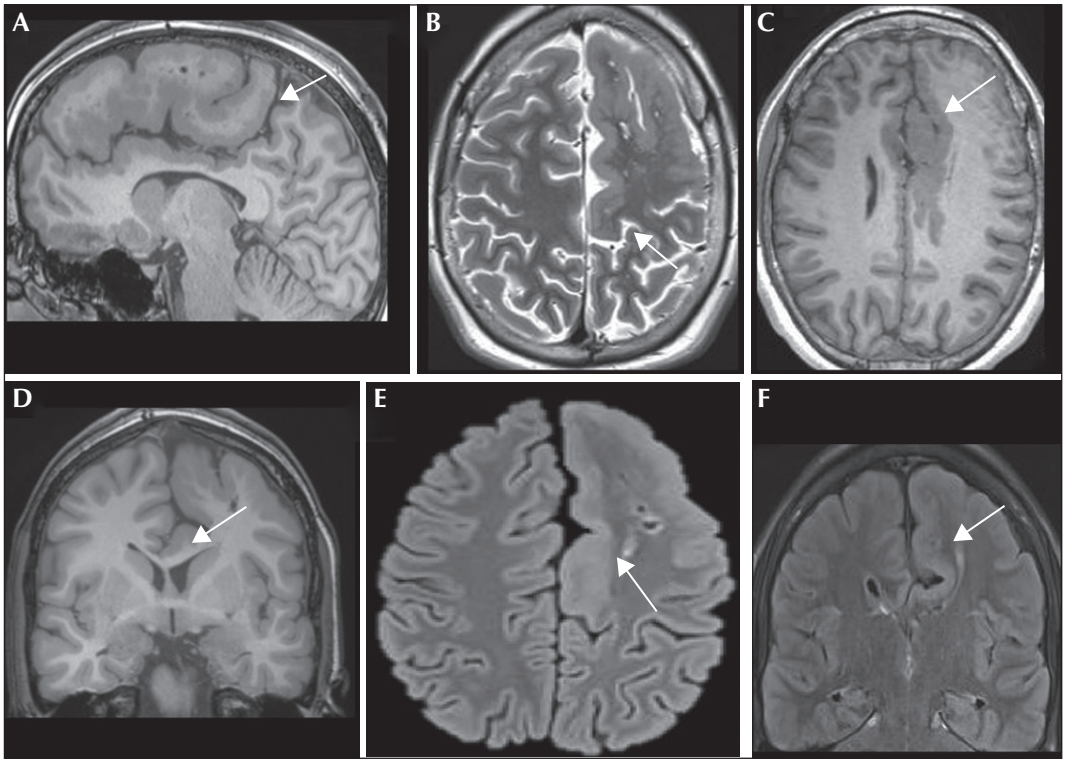

Figure 1. (A, B) Mesial and lateral view of the dysplastic left frontal lobe; arrows show the borders, and marginal and postcentral sulcus, respectively. (C) Abnormal gyration pattern resembling polymicrogyria. (D) Moderately enlarged lateral ventricle and slight midline shift. (E) Abnormal white matter signal from hypomyelination and gliosis. (F) Transmantle sign.

relapse and by a new period of remission of two years (when valproate added) and again relapse, a year ago. Introduction of levetiracetam and lacosamide was followed by an increase in seizure frequency. Surgical treatment was extensively discussed with the patient, but probable resulting hemiparesis was unacceptable for him and he chose to continue with medical treatment. Only recently, he was prescribed lamotrigine, with a currently gradual increase of the dose.

Discussion

This case highlights the continuity of the manifestation of the HME/ FCD type IIb spectrum, both radiologically and clinically. Microscopically, FCD IIb and HME show striking morphological similarities and both disorders involve activation of the mTOR pathway and exhibit phosphorylated tau expression (Sarnat and Flores-Sarnat, 2015; Najm *et al*., 2018). From a neuropathological perspective, the most important distinction between HME and FCD is their relative extent or the size/volume of the lesion (Najm *et al*., 2018; Mühlebner *et al*., 2019). If the somatic mutation of mTOR pathway genes is first expressed in a late mitotic cycle, the number of abnormal clones is smaller and the resulting lesion is more focal, involving a single gyrus, such as FCD IIb. If the mutation is expressed in a somewhat earlier cycle, the lesion is more extensive and may involve several adjacent gyri or part of one hemisphere as more extensive FCD IIb or limited HME; the involvement of an earlier mitotic cycle can produce HME of the entire hemisphere (Sarnat and Flores-Sarnat, 2014; D'Gama *et al*., 2017). Aforementioned studies provide a solid support for the concept that FCD and HME exist as a space-time continuum of pathology whose manifestation is dictated by space (the cell location and type affected by a somatic mutation) and time (the developmental stage at which the mutation occurs) (Jansen, 2019).

Neuroimaging in our patient showed dysplastic parenchyma of the entire left frontal lobe, which was separated from the rest of the brain by a deep central sulcus. The extent of the lesion represents a transition between FCD, which is typically confined to single gyrus, and HME, which involves the entire hemisphere. Intermediate malformations have been reported, but they usually comprise the temporal, parietal, and occipital lobes of one cerebral hemisphere, and are designed as partial (posterior cortex) HME (D'Agostino *et al*., 2004). On the contrary, localization of the malformation in our patient in the frontal lobe is similar to FCD type IIb, which is seldom seen in the occipital and parietal lobes, but has a predilection for the frontal lobes (Fauser *et al*., 2006; Rácz *et al*., 2018).

Clinical characteristics of our patient embody features typical of both FCD and HME. The age of epilepsy onset in our patient is similar to the mean age reported for FCD (nine years in our patient and eight years for patients with FCD) (Rácz *et al*., 2018). It is slightly higher than the range (three to seven years) of the other three cases with frontal lobe HME (Ono *et al*., 2016). Whereas the age spectrum is quite broad for patients with posterior cortex HME (one day to 10 years; mean: one year) (D'Agostino *et al*., 2004), patients with classic HME notably tend to develop epilepsy earlier (the onset is in the neonatal period, sometimes from the first day of life) (Flores-Sarnat, 2002). The relapsing-remitting pattern of seizure control in our patient has been established in about 17% of the patients with FCD, who showed transient responsiveness (>one-year seizure freedom) to antiepileptic drug therapy either after initial therapy (50%) or later in the course of epilepsy (50%) (Fauser *et al*., 2006). The typical patient with HME in published series has intractable focal epilepsy immediately from onset (Flores-Sarnat, 2002). Seizures were well controlled by medication in three patients with frontal HME.

In patients with HME, overt hemiparesis can be evident from the neonatal period or can be mild or absent. Apart from right-hand clumsiness, no signs of hemiparesis or other abnormalities on neurological examination were seen in our patient, similarly to three other patients with frontal HME. Stagnation of intellectual development is common in patients with HME (including partial variations), and they may be mild to severely intellectually disabled, while cognitive impairment is rather uncommon in the patients with FCD. Although lacking cognitive assessment, our patient's ability to attend regular school positioned him within the normal functional range.

Similar to other reported cases of malformation confined to the frontal lobe, radiological findings in our patient were consistent with those in HME; thickening of the cortex with an abnormal gyral pattern resembling polymicrogyria, blurring of the grey-white matter boundary, increased volume of white matter, and a broadened genu of the corpus callosum (Ono *et al*., 2016). In terms of differential diagnosis, FCD does not show the broadening of the corpus callosum, increased white matter volume, or lobar enlargement. Thus, the combination of volume enlargement and abnormal white matter signal from hypomyelination and gliosis are important MRI characteristics of HME (Shrot *et al*., 2018). Mild white matter changes or normal appearance of white matter with no volume changes or lobar volume reduction, on the other hand, suggest cortical dysplasia (Santos *et al*., 2014; Shrot *et al*., 2018). The white matter signal alteration tapering towards the ventricle (transmantle sign), revealed on

our patient's MRI, is actually almost exclusively found in FCD type II (Colombo *et al*., 2009).

Nonetheless, one limitation of our study is the lack of surgical brain specimens to confirm a histopathological diagnosis and provide molecular-genetic data which would enlighten the nature of this lesion.

In conclusion, a localized malformation in the unilateral frontal lobe in our patient represents an intermediate case within the FCD type II/ HME range. Localization of the lesion in the frontal lobe as well as clinical characteristics (childhood onset, relapsing-remitting epilepsy, without hemiparesis and overt cognitive impairment) are more consistent with FCD, while a range of MRI features is shared between HME and FCD type II. □

Disclosures.
None of the authors have any conflict of interest to declare.

References

Blümcke I, Thom M, Aronica E, *et al*. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011; 52(1): 158-74.

Colombo N, Salamon N, Raybaud R, Özkara C, Barkovich J. Imaging of malformations of cortical development. *Epileptic Disord* 2009; 11(3): 194-205.

D'Agostino MD, Bastos A, Piras C, *et al*. Posterior quadrantic dysplasia or a characteristic brain malformation. *Neurology* 2004; 62: 2214-20.

D'Gama AM, Woodworth M, Hossain A, *et al*. Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias. *Cell Rep* 2017; 21(13): 3754-66.

Fauser S, Huppertz HJ, Bast T, *et al*. Clinical characteristics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients. *Brain* 2006; 129(7): 1907-16.

Flores-Sarnat L. Hemimegalencephaly: Part 1. Genetic, clinical, and imaging aspects. *J Child Neurol* 2002; 17(5): 373-84.

Jansen LA. The space-time continuum of cortical dysplasia. *Epilepsy Curr* 2019; 19(1): 54-6.

Mühlebner A, Bongaarts A, Sarnat H, Scholl T, Aronica E. New insights into a spectrum of developmental malformations related to mTOR dysregulations: challenges and perspectives. *J Anat* 2019; 235(3): 521-42.

Najm IM, Sarnat HB, Blümcke I. Review: the international consensus classification of focal cortical dysplasia - a critical update 2018. *Neuropathol Appl Neurobiol* 2018; 44(1): 18-31.

Ono Y, Saito Y, Maegaki Y, *et al*. Three cases of right frontal megalencephaly: clinical characteristics and long-term outcome. *Brain Dev* 2016; 38(3): 302-9.

Rácz A, Muller AM, Schwerdt J, Becker H, Vatter A, Elger C. Age at epilepsy onset in patients with focal cortical dysplasias, gangliogliomas and dysembryoplastic neuroepithelial tumors. *Seizure* 2018; 58: 82-9.

Santos AC, Escorsi-Rosset S, Simao G, *et al*. Hemispheric dysplasia and hemimegalencephaly: imaging definitions. *Childs Nerv Syst* 2014; 30(11): 1813-21.

Sarnat HB, Flores-Sarnat L. Morphogenesis timing of genetically programmed brain malformations in relation to epilepsy. *Progr Brain Res* 2014; 213: 181-98.

Sarnat HB, Flores-Sarnat L. Infantile tauopathies: hemimegalencephaly; tuberous sclerosis complex; focal cortical dysplasia 2; ganglioglioma. *Brain Dev* 2015; 37(6): 553-62.

Shrot S, Hwang M, Stafstrom C, Huisman T, Soares B. Dysplasia and overgrowth: magnetic resonance imaging of pediatric brain abnormalities secondary to alterations in the mechanistic target of rapamycin pathway. *Neuroradiol* 2018; 60(2): 137-50.

TEST YOURSELF

(1) Focal cortical dysplasia and hemimegalencephaly share the following features:

A. Dysplastic megalocytic neurons, balloon cells, dyslaminated cortical architecture, and abnormal glial cells
B. Are caused by mutations in the mTOR pathway genes
C. Are associated with refractory epilepsy
D. All of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".