Epileptic Disord 2010; 12 (3): 169-71

Are some focal cortical dysplasias post-migratory cortical malformations?

Roberto Spreafico

Epilepsy Clinic and Experimental Neurophysiology Unit, Fondazione IRCCS, Istituto Neurologico "C. Besta", 20133 Milano, Italy
<spreafico@istituto-besta.it>

The development of the human cortex is a spatially complex, tightly regulated, ordered process, operating between the fifth and approximately 24th week of gestation. Studies and debates on the developmental events that shape the neocortex date back to the first pioneers of neuroscience. However, during the last decade, an increasing bulk of literature has proved that the mechanisms underlying cortical development are much more complex than previously thought, and the rather simplistic schemes conceived in the past are now under permanent revision.

Despite the very fast pace of identification of genes involved in cortical development, cell-specific gene expression analysis is not available nor is the knowledge about the intimate mechanisms that govern corticogenesis. Nevertheless, both genetic and environmental mechanisms have been identified in corticogenesis and three essential developmental steps are recognized: proliferation, migration and differentiation. This applies to all mammalian species including humans, whose brains reach maximal growth increase and complexity only during the last two months of gestation. Any disturbance, regardless of the cause, can lead to a wide range of morphological alterations, from severe brain malformations to local disruption of cortical structure. Improvement of our knowledge about basic mechanisms of corticogenesis require, therefore, a continuous debate and revision of concepts, nomenclature and classification schemes. In recognition that more complex mechanisms are involved in corticogenesis, these pathologies, originally defined as Neuronal Migration Disorders (NMDs), are now listed under the less ambiguous term of Malformations of Cortical Development (MCDs). MCDs represent a wide group of brain alterations encompassing many disorders with different pathogenesis, genetic abnormalities, structural neuropathological defects and clinical features. Notwithstanding, MCDs are frequently associated with neurological deficits and represent one of the most common causes of refractory epilepsies.

Increasing advances in neuroimaging techniques, the refinement of neuropathological procedures and the recognition of several molecular pathways and genetic impact of MCD have led to the necessity for new classification schemes also useful in clinical practice. In consideration of the three main developmental processes, Barkovich *et al*. (2005) developed a classification pointing out the intricate aspects of cerebral development. Among the disparate group of MCDs, Focal Cortical Dysplasias (FCDs) have increasingly attracted the interest of many scientists since the first description in 1971 by Taylor *et al*. As a result, high definition imaging technologies and post-processing protocols have helped to redefine previously classified cryptogenic epilepsies as symptomatic. This became the object of many investigations since some, but not all, FCDs can be successfully treated with surgery. This strategy requires a sophisticated classification system combining neuropathological characteristics, electroclinical data, imaging presentation and molecular phenotypes which reliably classify different FCD variants.

In Palmini's classification, two groups of FCD, type I and type II, are recognized (Palmini *et al.*, 2004). Imaging features, electroclinical presentation and neuropathological data clearly depict type II FCD as a separate clinicopathological entity with a good clinical correlation and post-surgical outcome. Whereas polymorphisms and loss of heterozygocity of the TSC1 gene locus have been detected in patients with type II (Becker *et al.*, 2002), no genetic abnormalities have been described in epilepsy patients with FCD type I whose electroclinical diagnosis, imaging identification and surgical outcome is still puzzling. In Palmini's FCD classification, type I includes a wide spectrum of histopathological alterations, and may frequently also associate with other principal lesions. Their aetiology remains, however, unknown. Experimental data from animal models revealed that postnatal injury induces epileptogenic cortical disorganisation (similar to human FCD) in the vicinity of the lesion (Ferrer, 1993; Timofeev *et al.*, 2010). The experimental data have been confirmed by neuropathological and clinical studies in young patients suggesting a remodelling of the cortex after early postnatal injury with neuropathological alterations similar to type I FCD (Lombroso, 2000; Marín-Padilla, 2002).

All these data indicate that cortical dysplasias might also occur in a period when neuronal migration is already accomplished and presumably result from regional, intrinsic and post-migrational cortical rearrangement. These post-migrational events indicate the high plasticity of the perinatal brain with its intrinsic capability to regenerate

doi: 10.1684/epd.2010.0331

(neurogenesis), reorganise and rewire neuronal circuitries (Duchowny *et al*., 2000). Furthermore, recent observations in surgical specimens obtained from adult temporal lobe epilepsy patients revealed a peculiar cortical dyslamination with abnormal neuronal orientation and aggregation in layers II and III (Thom *et al*., 2009). These features were always observed in TLE patients with hippocampal sclerosis and are similar to those previously classified as FCD type I (Garbelli *et al*., 2006 ; Tassi *et al*., 2009). Thom *et al*. (2009) proposed that early, frequent and intractable seizures, even originating from the hippocampus, could interfere with the process of late neocortical temporal development and maturation, resulting in an acquired (post-migrational) dysplastic pathomechanism. This interpretation is supported by the observation that development and maturation of the neocortex continues after birth into adolescence and that the postnatal development of the cerebral cortex depends on inputs from other cortical areas (Guillery, 2005). Based on both experimental and clinical data, two different types of post-migratory dysplasias can be suggested in humans. The first may evolve during the perinatal period. Cortical alterations may reflect a response to injury in the developing cortex. The second, late onset dysplasia, could evolve from continuous epileptic discharges in hippocampal sclerosis which interfere with postnatal maturation in temporal lobe neocortical circuits.

In this issue of the journal, Blümcke *et al.* compared MRI with histopathological findings in a series of 19 children suffering from early onset, intractable severe epilepsies and psycho-motor retardation (Blümcke *et al*., 2010). They observed a significant correlation between multilobar volume loss, ipsilateral to the epileptogenic hemisphere, with the histopathological occurrence of microcolumnar disorganisation in the resected neocortex. They proposed a distinct FCD type I variant characterized by cortical hypoplasia and vertical architectural disorganisation. The interesting pathogenetic hypothesis suggested by the authors is inspired by the "radial unit lineage model" of corticogenesis (Rakic, 2009).The microcolumnar organisation represents the primordial cortical organisation and is related to the "inside-out" sequence of normal neuronal migration. However, our current concept of migrational defects is generally ascribed to only a restricted and early (prenatal) window of time for the developing cortex. Recent embryological data show that in subsequent periods of cortical development, horizontal rearrangement of radially migrating neurons take place and the original microcolumnar organisation disappear to be replaced by horizontal cortical lamination, as observed in full term infants and adults. The persistency of microcolumnar organisation observed in young epileptic patients by Blümcke *et al.* might represent a failure of the mechanisms involved in the horizontal redistribution of post-(radially) migrated neurons.

It is interesting to note that the persistent vertical microcolumnar organisation is particularly evident in the supragranular layers composed of the last migrated cohort of neurons in close vicinity to the reelin secreting Cajal-Retzius cells. These ancestral neurons have been demonstrated to be crucial in attracting neuroblasts in a correct position during migrational events, but also in the correct cell position in horizontal layers (Meyer, 2001). These data need to be confirmed but might represent a first step towards a possible explanation of the persistent microcolumnar organisation described by Blümcke and co-workers.

This peculiar FCD variant should be considered as distinct from other subtypes. It not only presents with a distinct neuropathological substrate and peculiar clinical feature but also requires proper investigation of underlying molecular signalling pathways that might be compromised in reshaping the maturing cortex from microcolumnar (vertical) organisation toward the mature horizontal cortical layering. □

References

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. *Neurology* 2005 ; 65 : 1873-87.

Becker AJ, Urbach H, Scheffler B, *et al*. Focal cortical dysplasia of Taylor's balloon cell type : mutational analysis of the TSC1 gene indicates a pathogenic relationship to tuberous sclerosis. *Ann Neurol* 2002 ; 52 : 29-37.

Blümcke I, Pieper T, Pauli E, *et al*. A distinct variant of focal cortical dysplasia type I characterised by magnetic resonance imaging and neuropathological examination in children with severe epilepsies. *Epileptic Disord* 2010 ; 12 : 171-9.

Duchowny M, Jayakar P, Levin B. Aberrant neural circuits in malformations of cortical development and focal epilepsy. *Neurology* 2000 ; 55 : 423-28.

Ferrer I. Experimentally induced cortical malformations in rats. *Childs Nerv Syst* 1993 ; 9 : 403-7.

Garbelli R, Meroni A, Magnaghi G, *et al*. Architectural (Type IA) focal cortical dysplasia and parvalbumin immunostaining in temporal lobe epilepsy. *Epilepsia* 2006 ; 47 : 1074-8.

Guillery RW. Is postnatal neocortical maturation hierarchical ? *Trends Neurosci* 2005 ; 28 : 512-7.

Lombroso CT. Can early postnatal closed head injury induce cortical dysplasia. *Epilepsia* 2000 ; 41 : 245-53.

Marín-Padilla M, Parisi JE, Armstrong DL, Sargent SK, Kaplan JA. Shaken infant syndrome : developmental neuropathology, progressive cortical dysplasia, and epilepsy. *Acta Neuropathol* 2002 ; 103 : 321-32.

Meyer G. Human neocortical development : the importance of embryonic and early fetal events. *Neuroscientist* 2001 ; 7 : 303-14.

Palmini A, Najm I, Avanzini G, *et al*. Terminology and classification of the cortical dysplasias. *Neurology* 2004 ; 62 : 2-8.

Rakic P. Evolution of the neocortex: a perspective from developmental biology. *Nat Rev Neurosci* 2009; 10: 724-35.

Tassi L, Meroni A, Deleo F, *et al*. Temporal lobe epilepsy: neuropathological and clinical correlations in 243 surgically treated patients. *Epileptic Disord* 2009; 11: 281-92.

Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. *J Neurol Neurosurg Psychiatry* 1971; 34: 369-87.

Thom M, Eriksson S, Martinian L, *et al*. Temporal lobe sclerosis associated with hippocampal sclerosis in temporal lobe epilepsy: neuropathological features. *J Neuropathol Exp Neurol* 2009; 68: 928-38.

Timofeev I, Bazhenov M, Avramescu S, Nita DA. Posttraumatic epilepsy: the roles of synaptic plasticity. *Neuroscientist* 2010; 16: 19-27.