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New concepts on developmental pathogenesis of Epileptogenic Focal Cortical Dysplasias

Background: Focal cortical dysplasias (FCD) are the principal cause of focal epilepsy in infants and children and are successfully treated by surgical resection and confirmed neuropathologically. The pathogenesis of these focal malformations of cortical development is elucidated by recent advances in neuroembryology and genetics. FCD type II is due to disturbances in the mTOR signaling pathway that causes dysmorphic neurons as well as abnormal brain architecture. During normal fetal brain development, keratan sulfate (KS) proteoglycan surrounds and isolates fascicles and tracts in the brain; KS also binds to neuronal somatic membranes where it repels excitatory but enables inhibitory axons; no KS surrounds dendritic spines, hence axodendritic synapses are excitatory.

Objective: To elucidate factors of pathogenesis of FCD and relate them to normal brain maturation.

Methods: 30 normal fetal and 12 infant and child brains, and also 10 cases of FCD were examined at autopsy or in surgical resections for epilepsy, with immunocytochemistry applied to tissue sections.

Results: FCD type I is persistence of normal fetal micro-columnar cortical architecture before horizontal lamination is superimposed during the second half of gestation. FCD II and hemimegalencephaly (isolated or associated with neurocutaneous syndromes) are the same disorder, the difference in extent depending in which of the 33 mitotic cycles of neuroepithelium the defective gene is first expressed. KS is altered in FCD and other brain malformations.

Conclusion: Neuroembryology and genetics are the bases for understanding pathogenetic mechanisms of brain malformations. Maturational arrest is a factor in FCD I. KS repels glutamatergic (excitatory) axons and facilitates GABAergic (inhibitory) axons, which explains why deep heterotopia often generate few or no seizures because of a KS barrier in the U-fibre layer that prevents integration into epileptic networks, why axosomatic synapses are inhibitory, and how KS isolates axonal fascicles to prevent exit or entry of axons along their trajectory.

Biography

Sarnat is professor of Paediatric Neurology and Neuropathology at the University of Calgary and Alberta Children's Hospital, Canada. He has devoted most of his career to developmental (fetal and neonatal) neuroanatomy and neuropathology, particularly in relation to brain malformations with clinical correlates and to the developmental neuropathology of epilepsy. He is one of 8 permanent member of the International League Against Epilepsy, Commission on Neuropathology. His 180 research publications include clinical studies that have become classics as the Sarnat grading scale of neonatal encephalopathies (1976) and the first description of neonatal olfactory reflexes (1978), as well as a recent long series of articles defining the sequence of synaptogenesis in the fetal brain and another series on development of the olfactory system. He is sole or co-author or editor of several textbooks and has contributed 120 chapters to textbooks and monographs. He serves on the editorial boards of 9 journals. He was keynote speaker at the 50th anniversary meeting of the *Canadian Association of Neuropathologists* and was the prestigious Bernard Sachs Lecturer in 2016 at the congress of the *Child Neurology Society* (U.S.A.). He lectures frequently throughout Europe, Latin America, Japan, Australia, U.S.A. and Canada. His wife and co-author of many publications, Dr. Laura Flores-Sarnat, is professor of Paediatrics and Clinical Neurosciences at the University of Calgary, formerly head of Child Neurology at the *Instituto Nacional de Pediatría*, a large university children's teaching hospital in Mexico City.

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