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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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Mario Navarrete Arellano

Hospital Central Militar, Mexico

Pediatric Robotic Surgery, experience and results of the first program in Mexico and Latin America

Statement of the Problem: There have been few reports on robotic general pediatric surgery. So far, the largest number of publications has been in the area of robotic urology. There is evidence that robotic surgery in children is safe. If conventional laparoscopy is used, the reconstruction procedures are very challenging, whereas robotic surgery overcomes its limitations and offers important advantages in complex surgeries. For example, the choledochal cysts have a incidence in the Asian population of 1 in 1000, about two thirds of cases reported in Japan. The surgical treatment is extirpation of the cyst with bilioenteric anastomosis in Roux-en-Y. I will emphasize this pathology, because robotic surgery is an excellent treatment alternative. More than 70 different surgical techniques have been published in children. There is a scarcity of publications in Latin America and our program is pioneer. The purpose to present the applications, share our experience and spread the robotic surgery in pediatric patients.

Methodology & Theoretical Orientation: A prospective, observational and longitudinal study was conducted from March 2015 to April 2019, that involved all pediatric patients that was treated with robotic surgery. The parameters evaluated were 13. I present the results of 256 procedures and 46 different robotic surgical techniques and in the discussion we compare our results with publications on general pediatric robotic surgery.

Conclusion & Significance: A enormous variety of surgeries can be safely performed, including complex surgeries: hepatobiliary, thoracic and tumor areas. It is important to offer children the advantages and safety of robotic surgery, it has been accepted slowly for children. It is possible to implement an effective program of pediatric robotic surgery in which multiple procedures are performed and with similar results to hospital centers in developed countries. It is very important to promote surgery of the future.

Biography

Mario Navarrete Arellano is a pecialist in Medical Pediatrics and Pediatric Surgeon, 29 years of experience in pediatric surgery, open surgery and conventional minimally invasive (thoraco-laparoscopy) and in the last 4 years has developed the expertise in robotic surgery (more than 200 procedures), in a public hospital of third level of care and performing private practice. Graduate from the Escuela Médico Militar (1975-1981) and Escuela Militar de Graduados de Sanidad (1982-1990), Universidad del Ejército y Fuerza Aérea Mexicanos. I hold the degree General Brigadier Surgeon Medical. Hospital trajectory: Added Medical Doctor, Head of Service, Head of Department, Head of Division of Pediatrics and Pediatric Surgery, Head of the External Assistence Area and Medical Subdirector in the Hospital Central Militar, Mexico City (1990-2018). Profesor and Chief of Courses of Pre and Postgraduate of Medical Pediatric and Pediatric Surgery, Escuela Médico Militar and Escuela Militar de Graduados de Sanidad, Universidad del Ejército y Fuerza Aérea (1985-2009). Mexico City. Advisor in 10 Works of Research (Thesis of Degree). More than 50 Publications in Medical Journals of the Specialty and Author or co-author of 4 Chapters in specialty books. Speaker or Profesor in more than 200 academic events, national or international. Member of 10 Societies, Associations, College and Academy National and International.

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Epidermal nevus syndrome and PIK3CA-Related Overgrowth Spectrum (PROS) in Neonates

Background: Epidermal nevus syndrome (ENS) is a spectrum within the broader category of neurocutaneous syndromes, as post-zygotic somatic mutations that affect the nervous system skin and other tissues. Mutation in the PIK signaling pathway, closely related to mTOR, causes alteration in cellular lineage, growth and morphogenesis. EN spectrum includes Proteus (PIK1) and CLOVES that clinically result in overgrowth of various tissues including the brain as hemimegaloencephaly (HME). HME also can occur as an isolated focal cerebral lesion, usually due to PIK3 mutation. The most frequent neurological manifestations of ENS are epilepsy, hemiparesis, cognitive/intellectual deficits and global developmental delay.

Objective: To correlate CNS dysmorphic overgrowth lesions with clinical presentation, especially in the neonatal period and infancy, in the context of neurocutaneous syndromes.

Methods: Synthesis of data on phenotype and clinical neurological presentation correlated with neuroimaging, EEG, neuropathological and genetic data, based upon personal experience with 20 ENS patients over years and extensive literature review.

Results: ENS exhibits a spectrum of phenotypes. Epilepsy is the earliest and most frequent neurological presentation, from the neonatal period or early infancy, as focal or multifocal seizures or infantile epilepsies including epileptic (infantile) spasms and Ohtahara syndrome. The most frequent underlying brain malformation is HME. Early diagnosis prenatally or in the neonate is important because prompt intervention with anti-seizure medications and mTOR inhibitors is feasible and justified for better outcome.

Conclusion: The presence since birth of nevi, cutaneous angiomata and overgrowth of extremities and visceral organs, sometimes more evident and progressive postnatally, is reason to perform brain MRI to exclude HME, and EEG to detect early subclinical epileptogenic foci. Early detection and anti-seizure treatment may delay or prevent the onset of severe infantile epilepsies. Detection of fetuses or neonates with HME by prenatal ultrasound or MRI may justify mTOR inhibitors (rapamycin) to arrest or attenuate progressive overgrowth.

Biography

Flores-Sarnat is professor of Paediatrics and Clinical Neurosciences at the University of Calgary and Alberta Children's Hospital, Canada. She is trained in both neonatalogy and paediatric neurology and is former Head of Paediatric Neurology at the Instituto Nacional de Pediatría, a large university children's teaching hospital in Mexico City. Her clinical and research interests are in the fields of fetal and neonatal neurology, brain malformations, neurocutaneous syndromes and early-onset epilepsy. She is the author or co-author of 60 research articles and many textbook chapters.

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