*Neurology Asia 2013; 18 (Supplement 1) : 5 – 7*

# Animal models of early life seizures and epilepsies

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### *Abstract*

Epilepsy can occur throughout the human life span, with peaks during early life and senescense/ageing. During development, epilepsy is often but not always diagnosed in association with cognitive and behavioral impairment, which may be the result of the underlying etiology and/or the consequences of epilepsy and treatments as factors of age and sex. Despite evolutionary and biological differences between rodent and human brain development, the possibility to model early life epilepsy and seizures in mice and rats helped the understanding of numerous factors involved in seizures pathophysiology: neurotransmitter maturation, inhibitory and excitatory pathways imbalance, genetic and epigenetic influences and the association between epileptic activity and learning deficits. Modeling early life epilepsies will improve the validity and reliability of translational studies in the search of the underlying neurobiological pathways and allow for identification and selection of better treatments.

## INTRODUCTION

The immature brain is more prone to seizures[1]. During this period of the human life-span, dedicated to brain function refinement, epileptogenic brain lesions, seizures and EEG discharges, and, indirectly, drugs effects and psychological factors, may have detrimental effects on the cognitive and behavioral development. Learning deficits and behavioral impairments could be directly related to the cause of the epileptic disease, and could also represent consequences of the epileptic activity. However, not all epilepsies lead to cognitive impairment. Despite the asynchronous brain development and different developmental processes [2-3] that need to be taken into account, the use of rodent animal models allowed studies on the developing brain that brought insights on the importance of factors like age and sex in the development of early-life epilepsy and its impact on the developing brain. Age-specific changes in the expression and function of GABA- and NMDA neurotransmitter systems were shown [3]. In the GABA signaling system, GABAa receptors broadcast sexually differentiating signals in the developing brain.[4] The present paper will briefly review the available models of early life epilepsy and seizures, the questions that should be asked and the pitfalls to avoid.

## MODELING EPILEPSY BY SEIZURES TYPE AND BY SYNDROME

Animal models of epilepsy, mostly developed in rodents, should be considered to belong to four different subgroups: models of specific epilepsy seizures types; models of chronic epilepsy; models proposed for electro-clinical syndromes; models designed to mimic epigenetic influences (special emphasis on temporal lobe epilepsy – TLE)[5].

Models of focal onset seizure type are the electrical and chemical kindling[6], tetanus toxin model[7], kainic acid model[8], pilocarpine model[9], and electrical stimulation.[10] Models of generalized onset seizures types are models of absence seizures, tonic or clonic seizures, and myoclonic seizures. It is also possible to model chronic epilepsy with a specific age-relationship (neonatal period, infancy, childhood, adolescence-adult); most of the early life models are genetic, like the epilepsy models of the neonatal period: familial neonatal seizures (KCNQ2 knockout mouse), early infantile epileptic encephalopathy (STXBP1 knockout mouse), and the pyridoxine-dependent epilepsy (TNAP-deficient mice); or like the severe myoclonic epilepsy of infancy (SCN1a knockout mouse). Interestingly few of these so-called early life epilepsy models develop epilepsy during the brain development period, but mostly at an adult

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age. The multiple-hit model of West syndrome (an epileptic encephalopathy of the infancy) is a symptomatic model of epileptic spasms and one of the few developing spontaneous seizures at an immature age. Other models of chronic epilepsies include epilepsy of distinctive constellation like temporal lobe epilepsy (TLE) (kainic acid model, pilocarpine model and kindling model), Rasmussen encephalitis (anti-GluR3 antibodies model) and epilepsia partialis continua (GABA withdrawal model, tetanus toxin model, epilepsies attributed and organized by structural-metabolic causes (Tuberous sclerosis complex and Tsc1 knockout model) and epilepsies of unknown cause (febrile seizures and the hyperthermia-induced models). Some models were designed to mimic epigenetic influences that may lead to epilepsy with a special emphasis on TLE, like the cortical malformation models, the hypoxia-induced seizures or the complex febrile seizures models.

Different scales exist to score severity and seizure stages in the different animal models, mostly based on behavioral expression: the scoring system for focal seizures with secondary generalization, with specific scoring for kindling in immature and adult rats, and for the KA-/pilocarpine induced seizures.[11-13] There exists also the scoring system for primary generalized seizures with forebrain origin.[14,15]

## EPILEPSY, EPILEPTOGENESIS, AND COGNITION IN CLINICAL AND TRANSLATIONAL STUDIES

There are various animal studies and parallel observations in humans of impaired neurophysiological mechanisms involved the epileptic process and the associated comorbidities like cognitive deficits. Animal studies have shown that that the consequences of seizures are age-specific in terms of neuronal loss, glial activation, neurogenesis and synaptic reorganization.[3] Status epilepticus (SE) in normal developing male rats does not usually induce hippocampal cell loss or synaptic reorganization in the dentate gyrus till after the third postnatal week.[16] Brain MRI obtained within few days after SE can identify which animals may go ahead and develop epilepsy.[17] This observation is now being explored in the FEBSTAT study to determine the long term effects of febrile SE in humans.[18]

## TRANSLATIONAL STUDIES AND THERAPY DEVELOPMENT IN INFANTILE SPASMS

West syndrome or infantile spasms syndrome is an epileptic encephalopathy of the infant, associating epileptic spasms, interictal aberrant EEG pattern called hypsarrythmia and usually very poor developmental outcome including autism spectrum disorder. The multiple hit model of infantile spasms is a symptomatic model displaying epileptic spasms at an immature age (post natal day 4), EEG pattern with ictal electrodecremental responses and learning deficits as well as autistic features.[19] Administration of pulse Rapamycin improved epileptic spasms and cognitive and behavioral disorders in the treated animals.[20] This example illustrates the importance of a novel approach of the early-life epilepsies, and the need for appropriate models, mimicking the epileptic disease and its comorbidities.

Only well-designed translational studies will help in understanding of the underlying pathological mechanisms and effects of age and gender on outcome; in defining the association genotype-phenotype for the different syndrome, and their variations, in identifying and testing new antiepileptogenic or symptomatic treatments. As shown, animal models help in the identification of biomarkers (reviewed in [3]). Eventually, as some of underlying causes may be preventable, the early identification of these biomarkers will allow for adequate medical and educational interventions.

## ACKNOWLEDGEMENTS

Dr. Moshé is funded by grants from NIH NS43209, NS20253, NS45911 and from the Heffer Family and the Segal Family Foundations. He is serving as Associate Editor of Neurobiology of Disease, and is on the editorial board of Epileptic Disorders, Brain and Development, Pediatric Neurology and Physiological Research. He receives from Elsevier an annual compensation for his work as Associate Editor in Neurobiology of Disease and royalties from 2 books he co-edited. He received a consultant fee from Eisai and a speaker's fee and travel expenses from GSK. Dr. Jequier Gygax is funded by grants from the Swiss National Science Foundation (PBLAP3-129421/1 and PBLAP3-137095) and from SICPA Foundation, Switzerland.

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