

## Is epileptogenesis a key to treatment of childhood epileptic encephalopathies?

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Despite the recent discovery of many newer and safer antiepileptic drugs (AEDs) the number of patients with drug resistant epilepsy remains at about 30%. Epilepsy is particularly devastating in the first years of life often causing mental retardation and autistic behavior, usually leading to epileptic encephalopathies. A better understanding of epilepsy development (epileptogenesis) in this group of patients may lead to successful prevention of drug-resistant epilepsy and its comorbidities (Barker-Haliski et al., 2015; Chapman et al., E-pub ahead of print).

Scientific basis for possible intervention has been established in recent animal genetic models of epilepsy. In their study, Yan et al. (2005) used an epileptic double mutant rat (SER; zi/zi, tm/tm) which after age 7–8 weeks spontaneously exhibits tonic and absence-like seizures in response to mild sensory stimulation. Three weeks before the expected time of seizure onset, from postnatal weeks 5 to 8, rats received levetiracetam at 80 mg/kg/day (i.p). The seizure assessment has been carried out in weeks 12 and 13 (5 weeks after termination of the administration), by clinical evaluation and conventional EEG recordings. The incidence of both tonic and absence-like seizures was significantly lower in levetiracetam treated group comparing with the control animals. This effect was suggested to be due to an antiepileptogenic rather than an antiseizure effect, as the half-life time of levetiracetam in plasma is short (2–3h in rats) after single and long term administration (Yan et al, 2005).

Another group of researchers performed the experiment in a genetic model of human absence epilepsy. Wistar Albino Glaxo/Rij rats, that exhibit spontane-

ous spike-wake complexes on electroencephalography and seizures at 3 months of life, were administered oral ethosuximide from day 21 to 5 months of age. On follow-up at 8 months, after several months of discontinuation of the treatment, the significant suppression of discharges and lower number of seizures was still documented (Blumenfeld et al., 2008).

Both Yan et al. (2005) and Blumenfeld et al. (2008) studies demonstrated that epilepsy prevention may be possible and that such a strategy could be considered in susceptible human cohorts. Indeed similar studies in humans carried out in selected groups of patients in the first year of life with a high risk of epilepsy, seem to corroborate the results obtained in animals.

Ville et al. (2002) identified a group of 16 infants with Sturge-Weber syndrome, the condition characterized by early onset of seizures and poor mental outcome. Preventative treatment of this group with phenobarbitone, the drug frequently used for neonatal seizures, resulted in decreased epilepsy ( $p < 0.01$ ) and mental retardation ( $p < 0.05$ ) incidence in comparison to 21 children treated in the standard manner (i.e. after the onset of clinical seizures).

The results are concordant with our results obtained in tuberous sclerosis complex (TSC) (Jozwiak et al., 2011). In a prospective study of 14 young infants who underwent regular EEG assessments every 4–6 weeks until 24 month of age, ten patients received a treatment with vigabatrin due to paroxysmal multifocal activity on EEG. The treatment was discontinued at 24<sup>th</sup> month, if no clinical seizures appeared. Six out of 10 children developed epilepsy despite of the medication. However, we demonstrated a lower incidence of drug-resistant

epilepsy and higher intelligence quotient (IQ) score at 24 months of life compared with 31 children treated in the standard manner, after clinical seizures, (7.1% vs 41.9%,  $p < 0.05$ ; and 92.3% vs 68.7%,  $p < 0.05$ , respectively). Moreover, in 8 out of 10 preventatively treated patients paroxysmal activity on EEG turned to normal at 24<sup>th</sup> month of age (Jozwiak et al., 2011).

There is a need of identification of further groups of patients with well defined high risk of epilepsy development and drug-resistant seizures. In these clinical conditions similar antiepileptogenic (not antiepileptic!) treatment, before the onset of clinical seizures, should be considered. With the increasing knowledge of epilepsy pathogenesis a specific treatment for a target cohort should be tailored.

However, in order to identify the groups with high risk of epilepsy we should better understand the processes underlying the epilepsies and identify potent reliable biomarkers of epileptogenesis (Moshe et al., 2015). Epileptogenic mechanisms, and thus biomarkers, are likely to be specific for many different causes of epilepsy and to specific stages of epileptogenesis. There is no one “universal” biomarker and whole epilepsy and for all epilepsies.

According to definition, “a biomarker for epileptogenesis is an objectively measurable characteristic of a biological process that reliably identifies the development, presence, severity, progression, or localization of an epileptogenic abnormality” (Pitkanen and Engel, 2014). The search of such biomarkers is ongoing. Among them are electrophysiological, pathologic, imaging, and molecular biomarkers. Currently such comprehensive studies on biomarkers are ongoing within the EPISTOP, the large-scale collaborative project within the 7<sup>th</sup> Framework Programme of European Community. EPISTOP is a prospective study of epileptogenesis in TSC infants, starting from its latent phase before seizures onset and extending to the development of drug-resistance and epilepsy neuropsychiatric comorbidities. The comprehensive analysis of possible epileptogenesis biomarkers in the EPISTOP project includes a wide range of clinical, electrophysiological, neuroimaging, neuropsychological and molecular (including genomics, transcriptomics, proteomics, metabolomics) investigations.

Prevention of epilepsy, and particularly childhood epileptic encephalopathy is an important goal for epileptologists and the importance of this approach has been recognized by the United States and European sci-

entific community (Baulac et al., E-pub ahead of print). The recent 13<sup>th</sup> ILAE Workshop on the Neurobiology of Epilepsy (WONOE) has been entirely dedicated to biomarkers of epileptogenesis. Antiepileptogenesis is a significant challenge for both pediatric and adult neurologists, requiring intensive research in epileptogenesis and biomarkers, which would enable preventive therapies for epilepsy and its comorbidities.

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