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Prevention of Epileptogenesis—A New Goal for Epilepsy Therapy

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Progress in epilepsy treatment in last decades of the twentieth century included a number of new antiepileptic drugs that were expected to reduce the number of patients with drug-resistant epilepsy. However, it soon became obvious that, in spite of the improving safety of antiepileptic treatment, the efficacy of new agents was not much better than the old drugs. The number of patients with drug-resistant epilepsy decreased little, and their outcome has not been improved.

The search for new therapeutic approaches and the emergence of clinically relevant animal models of epilepsy led to a renewed interest in the process of epileptogenesis. This cascade of molecular and cellular alterations (including changes in expression and function of receptors and ion channels) begins with an insult, brain injury, or genetic predisposition. There is often a latent period lasting weeks to months before the onset of seizures, followed by the development of clinical epilepsy and its comorbidities. This latent period of epilepsy development may offer a time window when an appropriate medication may stop or modify the epileptogenic process.

Recent animal studies using the genetic models proved that early (antiepileptogenic) therapeutic intervention during this latent period might prevent the development of epilepsy. In an epileptic double mutant rat (spontaneously epileptic rat; zi/zi, tm/tm) that presents recurring tonic and absence-like seizures in response to mild sensory stimulation, Yan et al.[1] used levetiracetam for three weeks before the expected time of seizure onset. Such preventative treatment with levetiracetam resulted in a significant decrease in the incidence of both types of seizures, indicating a disease-modifying effect.[1] Another genetic model of human absence epilepsy was used by Blumenfeld et al.[2] Wistar Albino Glaxo/Rij rats that exhibit spontaneous spike-wave discharges on electroencephalography (EEG) were treated with oral ethosuximide from postnatal day 21 to 5 months of age. Early treatment with ethosuximide led to a persistent suppression of seizures, even several months after therapy withdrawal. Prolonged antiepileptogenic treatment in this genetic model had a beneficial effect on white matter microstructure in Wistar Albino Glaxo/Rij rats as observed by diffusion tensor imaging studies.[3] These experiments with ethosuximide and levetiracetam in genetic models seem to demonstrate that epilepsy prevention is possible and that antiepileptogenic treatment may provide a new strategy for preventing epilepsy in susceptible individuals.

Several completed clinical trials in humans have demonstrated that administration of conventional antiepileptic drugs, such as phenytoin, phenobarbital, carbamazepine, or valproate, in patients after traumatic brain injury failed to prevent the development of epilepsy.[4] However, it seems likely that these studies were not properly designed to answer the question at hand, and the drugs were not selected to have antiepileptogenic activity.[5]

The immature brain seems to be especially vulnerable to seizures, but it may also be particularly susceptible to antiepileptogenic treatment. Talos et al.[6] used a rodent model of acute hypoxia-induced neonatal seizures to determine how seizures alter mTOR complex 1 signaling, contributing to epileptic networks and autistic-like behavior in later life. They demonstrated that inhibition of mTOR complex 1 immediately before and after seizures reversed an early increase in glutamatergic neurotransmission and seizure susceptibility and attenuated later life epilepsy and autistic-like behavior.

The impact of effective antiepileptogenic treatment on the immature brain is particularly apparent in children less than two years of age. Clinical settings provide an especially good opportunity to prevent epilepsy and its comorbidities in some genetic or developmental defects with a high risk of epilepsy during the first years of life. Prophylactic treatment with phenobarbitone of 16 infants with Sturge-Weber syndrome resulted in decreased epilepsy ($P < 0.01$) and mental retardation ($P < 0.05$) in comparison to 21 children treated in the standard manner (i.e., after the onset of

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clinical seizures).[7] A similar beneficial effect of preventative treatment has been observed in our study in infants with tuberous sclerosis complex (TSC). A prospective study of 14 children treated with vigabatrin due to paroxysmal activity on EEG in the first months of life demonstrated a lower incidence of drug-resistant epilepsy and higher intelligence quotient score at 24 months of age compared with 31 traditionally treated children (7.1% versus 41.9%, $P < 0.05$; and 92.3% versus 68.7%, $P < 0.05$, respectively).[8]

The recently published "practical clinical definition of epilepsy" made also a step forward toward antiepileptogenic treatment by allowing the diagnosis of epilepsy after a single seizure in many situations with a probability of another seizure exceeding 60%.[9] However, there are still no recommendations for pre-emptive management of specific groups of patients with a very high incidence of epilepsy, well recognized natural course of the disease, and established severe epilepsy comorbidities such as mental retardation and autism. In conditions such as TSC, Sturge-Weber syndrome, Angelman syndrome, and Rett syndrome with an incidence of epilepsy over 60% in the first year of life, the antiepileptogenic treatment should be considered before the onset of clinical seizures, when epileptogenesis is early in progress.

A search of valid biomarkers to aid the identification of a point of no return in the epileptogenesis process is a major challenge for clinicians. In our experience with over 50 TSC infants followed since soon after birth with video EEGs performed every 4 weeks, those who developed paroxysmal activity demonstrated seizures within 2-3 weeks.[10] A determination of EEG characteristics as well as the molecular and neuroimaging biomarkers allowing identification of children with high risk of epilepsy is critical. Currently, such studies are ongoing within the long-term, prospective study evaluating clinical and molecular biomarkers of EPIlleptogenesiS in a genetic model of epilepsy—Tuberous SclerOsis ComPlex (EPISTOP), the large-scale collaborative project within the 7th Framework Programme of European Community. EPISTOP is a multicenter, 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 EPISTOP project includes a wide range of clinical, electrophysiological, neuroimaging, neuropsychologic, and molecular (genomics, transcriptomics, proteomics, metabolomics, epigenetics) investigations. The project has just begun and will last for five years.

Prevention of epilepsy in individuals at risk or the modification of the disease outcome is one of the major United States The National Institute of Neurological Disorders and Stroke/ National Institutes of Health Epilepsy Research benchmarks and also a research priority of the European scientific community. Such a goal is particularly meaningful for pediatric neurologists, the physicians who are often in the optimal position to alter the natural course of disease and improve the quality of life of their patients and their families.

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