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INVITED EDITORIAL

Can we prevent epilepsy? Yes, we can!

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Abstract

Epilepsy appears in 1% of global population and despite a progress in medicine still around 30% of patients have drug-resistant epilepsy. In recent years increasing attention is paid to possibility of epilepsy prevention. Candidate groups for such treatment are eagerly looked for. One of them is tuberous sclerosis complex (TSC).

Keywords: prevention · tuberous sclerosis complex · epilepsy

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Epilepsy is one of the most common neurological illnesses, known to appear in around 1% of the global population. Six million people have epilepsy in Europe alone. It may start at any age, but most often occurs in early childhood or people over 60 years old. Peak incidence is reported in the first 12 months of life.

The etiology of epilepsy remains unknown in up to 50% of cases. Therefore, for majority of patients with epilepsy their treatment is focused on seizure prevention rather than treating the underlying cause. This strategy helps about two-thirds of the patients to enjoy a seizure-free life, whereas about 30% of them suffer from drug-resistant seizures. Epilepsy in infants and children is particularly harmful, with 50% of these patients suffering from significant comorbidities e.g. developmental delay, learning disabilities and autism spectrum disorders.

Yet fifteen years ago nobody dared to claim that epilepsy may be preventable. Since the beginning of modern neurology (second half of XIX century), neurologists were taught to start treatment after clinical seizures, usually after 2 unprovoked seizures that occurred > 24 hours apart. However, such approach proved unsuccessful and resulted in many cases of drug-resistant epilepsy. Unsatisfactory results of treatment with standard antiepileptic medication led researchers to seek new therapeutic approaches. A new practical and "operational" definition of epilepsy introduced by the International League Against Epilepsy (ILAE) allows physicians to diagnose epilepsy when the patient had at least 2 unprovoked seizures > 24 hours apart or 1 unprovoked seizure with >60% risk of having another seizure during the next 10 years [1]. However, epilepsy does not start with first clini-

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cal seizure. It begins much earlier, during an insult to the central nervous system (CNS), e.g. stroke, inflammation or a genetic mutation. This process of changes in the brain leading to seizures is called epileptogenesis. First clinical seizures occur weeks, months or even years after the original insult. With recognition of individuals at high risk of epilepsy we may try preventing its development.

Some of the pre-clinical models of epilepsy have demonstrated that certain antiepileptic drugs may prevent or alleviate epilepsy when administered before seizures [2-3]. Clinical application of this concept in humans led to several trials assessing the effectiveness of these drugs in epilepsy prevention among patients after severe traumatic brain injury [4-6], stroke [7] or craniotomy [8-9]. Unfortunately all of these trials demonstrated that the standard antiepileptic drugs lack anti-epileptogenic effects. This could be partially explained by the inclusion of patients who had different risk of developing epilepsy, therefore highlighting the need to find reliable and clinically applicable biomarkers of epileptogenesis.

A better, human model for a study on epilepsy preventiion is offered by tuberous sclerosis complex (TSC), due to its genetic homogeneity and early age of epilepsy appearance. TSC is a common autosomal dominant neurocutaneous disorder occuring in approximately 1/6000 people. Pathogenesis of the condition is caused by loss-of-function germline mutations in either of the tumor suppressor genes *TSC1* or *TSC2*. Both mutations lead to hyperactivation of the mTOR pathway, which was demonstrated to contribute to epileptogenesis after traumatic brain injury, neonatal hypoxia or to kainate-induced status epilepticus [10-11]. About 90% of patients with TSC develop epilepsy during their lifetime and in a prospective study of children followed since birth, about 71% of them developed epilepsy in the first 2 years of their life [12]. Approximately 65% of those with epilepsy have drug-resistant epilepsy. In the group of patients presenting with seizures in the first year of life, up to 82% later develop intellectual disability and ~40% are diagnosed with autistic behaviours [13].

In 2011 our group at the Children's Memorial Health Institute in Warsaw published first results of an epilepsy prevention trial among infants with TSC. Forty-five infants who were diagnosed with TSC early in life were divided in two groups: standard (31 children) and prevention (14 infants). In the standard group the antiepileptic treatment was initiated after the first seizure. Patients in the prevention group were given antiepileptic medication after paroxysmal epileptic discharges were seen in their electroencephalography (EEG, repeated out every 4 to 6 weeks), though before the clinical onset of seizures. At 24 months of age, patients in the prevention group were more often seizure-free (93% vs 35%; $p = 0.004$), had lower incidence of drug-resistant epilepsy (7% vs 42%; $p = 0.021$) and fewer of them required multiple antiepileptic (21% vs 55%; 0.039) than those in the standard treatment group. Also intellectual disability was significantly more frequent and severe in the standard treatment vs prevention group (48% vs 14%; $p = 0.031$; mean IQ score 68.7 vs 92.3; $p < 0.05$) [12].

The results of this study influenced the current European recommendations on epilepsy management in TSC, which recommend regular EEG surveillance in infants with TSC and initiating antiepileptic treatment within the first 24 months of age when epileptiform discharges occur on EEG but before clinical seizure [14-15]. However, our results required confirmation in a large prospective randomized trial.

The EPISTOP project (NCT02098759) was a large European Union- funded study, whose aim was to examine the risk factors and biomarkers of epilepsy. Part of this project included a multicenter clinical trial assessing preventive and standard antiepileptic treatment. It included infants with a definite diagnosis of TSC, assessed from birth up to the age of 24 months with serial EEG, imaging and laboratory tests. In this study, 94 infants with TSC but without seizure history were observed with monthly video EEG and received vigabatrin either as conventional antiepileptic treatment (initiated after the first electroencephalographic or clinical seizure) or preventively when epileptiform was detected in EEG before the clinical onset of seizures. After 24 months of observation it was reported that preventive treatment reduced the risk of clinical seizures ($p = 0.032$), drug-resistant epilepsy ($p = 0.022$) and infantile spasms (OR = 0, $p < 0.001$) [16]. Similarly, an NIH-sponsored preventive study on epilepsy in TSC (the PREVENT trial), was launched in 2016 in the United States and the initial results are expected in 2021. In a 2019 survey of 61 epilepsy centers that provide care to patients with TSC, 70% conduct regular EEG monitoring in infants and 51,7% apply preventive treatment [17].

To answer the question stated in the title: yes, epilepsy can be prevented. Albeit, at the present moment this is possible only in very selected groups of patients with epilepsy due to a CNS insult with a known natural course of disease, as it is the case with TSC. The search of reliable biomarkers enabling early recognition of individuals with high risk of developing epilepsy is essential and still ongoing. Currently the meetings on prevention of epilepsy are a constant part of the American Epilepsy Society's annual meetings and mark a new trend in the approach to epilepsy treatment.

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