REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 3, pages: 190–193
DOI: 10.5603/PJNNS.a2019.0022

ISSN 0028–3843

Prevention of epilepsy in humans – truth or myth? The experience from Sturge-Weber syndrome and Tuberous Sclerosis Complex

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Abstract

Introduction. Epilepsy is a chronic neurological disease, usually decreasing the quality of life and often resulting in other comorbidities e.g. cognitive impairment in children. Despite the recent discovery of new antiepileptic drugs, roughly one in three patients suffers from drug-resistant seizures. Therefore, the prevention of epilepsy is becoming one of the most important challenges in medicine. Is it, however, in fact possible to prevent epilepsy?

Clinical reflections and implications. We present the results of preventive antiepileptic treatment in children with Sturge-Weber syndrome and Tuberous Sclerosis Complex as examples of the possible prevention of epilepsy and epilepsy-associated cognitive impairment in children.

Key words: epilepsy, prevention, tuberous sclerosis, Sturge-Weber

(Neurol Neurochir Pol 2019; 53 (3): 190–193)

Epilepsy affects approximately 50 million patients worldwide, with an incidence in paediatric patients that varies from 3.4 to 5.8 per 1,000 [1]. Effective epilepsy treatment and swift seizure cessation are especially important in children in whom uncontrolled seizures deteriorate the psychomotor functions, which leads to cognitive impairment and reduced quality of life in adulthood [2, 3]. Regardless of the immense progress in epilepsy treatment that has been made in recent years, drug-resistant epilepsy still afflicts roughly 30% of patients [4]. Therefore to the goal should be to try to prevent epilepsy. The question is whether the prevention of epilepsy is truly possible?

It has been documented that the process of epilepsy development (epileptogenesis) begins with an insulting/triggering factor (i.e. genetic mutation, injury, metabolic disease). This is followed by a latent period of changes in protein expression and ion channel functioning, and finally manifests with clinical seizures [5]. However, the epileptogenic process does not end with the occurrence of clinical epilepsy, but persists beyond the initial seizures, leading to the development of drug-resistant epilepsy and epilepsy-related comorbidities [5]. Thus, a better understanding of epileptogenesis may lead to the development of new, antiepileptogenic (AEG) therapies. There is an important difference between the terms antiepileptic (AED) and antiepileptogenic (AEG) drugs. AEDs (e.g. phenytoin, carbamazepine) are implemented after seizure onset and reduce seizure frequency and severity but do not influence epileptogenesis [5, 6]. On the other hand, AEGs may be introduced before or after epilepsy onset, and they change the natural course of epilepsy by counteracting epileptogenesis by prevention, seizure modification, reduction or prevention of the progression of epilepsy, or curing. Therefore, currently, the terms antiseizure (ASD) or anticonvulsant, rather than antiepileptic drug (AED) are beginning to be used in order to better distinguish the antiepileptogenic from the antiseizure effects of action [6].

In the light of recent studies on epileptogenesis, a first step to prevent epilepsy is to identify patients with a high risk of epilepsy development before the occurrence of clinical

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seizures. It is well known that patients after traumatic brain injury or stroke have an increased risk of epilepsy [7, 8]. However, objective studies on epileptogenesis and the possibility of its prevention are difficult in these groups of patients due to their considerable heterogeneity in terms of their aetiology, epilepsy risk, and the variety of environmental and individual factors that influence epileptogenesis [5, 7, 8].

On the other hand, some paediatric genetic diseases are highly associated with early-onset epilepsy, leading to more homogenous groups, and patients may be diagnosed before the development of clinical seizures, which enables a preventive intervention. Therefore, such children may be a perfect group for possible preventive antiepileptogenic treatment and studies of epileptogenesis.

Sturge-Weber syndrome (SWS) is a vascular neurocutaneous disorder with an incidence of 1 in 20,000–50,000 live births and it is characterised by a very high overall risk of epilepsy, that reaches 80-90% in the first two years of life [9, 10]. Due to a characteristic facial naevus, SWS can be diagnosed early, before epilepsy [11]. The study of Ville et al. demonstrated that preventive treatment with phenobarbital in SWS patients significantly decreased the incidence of epilepsy and delayed development compared to the control SWS group treated after first seizures [12]. The presence of developmental venous anomalies and decreased brain tissue perfusion leading to anoxic brain injury are the major contributory factors to epileptogenesis in SWS [13–15]. Early identification of potential predicting factors, combined with prophylactic antiepileptogenic therapy, may significantly improve the clinical outcome and life quality of patients.

Another paediatric model for possible antiepileptogenic intervention is tuberous sclerosis complex (TSC). This is a genetic neurocutaneous disorder with a high risk of early onset epilepsy (70–90%) associated with cognitive impairment (50–60% of TSC patients) and autistic behaviour [16]. TSC is more frequent than SWS, affecting 1 in 6,000 people and can be diagnosed very early, before clinical seizures, and even prenatally [16, 17]. The first seizures in TSC usually occur within first two years of life, mostly at the age of 4–6 months, and it has been proved that epileptiform discharges in electroencephalography (EEG) precede clinical seizures in TSC infants, being a good predictive factor for preventive treatment [18–20]. Based on the evolution pattern from epileptic EEG record to clinical seizures, we performed in our previous study regular EEG studies in infants with TSC and introduced preventive treatment with vigabatrin when ictal discharges occurred in EEG, but before clinical seizures [21]. At the age of 24 months, significantly more children in the preventive group were seizure-free compared to the standard group treated after clinical seizures (35% *vs* 93%, $p = 0.004$). Moreover, fewer children in the preventive cohort had drug-resistant epilepsy (7% *vs* 42%, $p = 0.021$). Also, of great importance for parents and children, the cognitive functioning of children treated before clinical seizures was significantly better (mean IQ: 92.3 *vs* 68.7, $p < 0.05$) and intellectual disability was also less frequent (14.3% *vs* 48.4%, $p = 0.031$) [21].

Besides the abovementioned treatment implications, new and interesting therapy approaches are emerging. Mutations in TSC1 or TSC2, encoding two tumour suppressor proteins of the mammalian target of rapamycin (mTOR) pathway, are known to cause TSC [22]. The mTOR signalling pathway is recognised as regulating a number of cellular processes required in the growth, metabolism, structure and interactions of neuronal cells [23]. Inactivation of one of the TSC genes results in overactivation of the mTOR pathway, leading to the development of benign tumours or hamartomas in multiple organs. In the majority of patients, the brain is one of the most affected organs, which results in epilepsy, developmental delay, and neurobehavioural or neuropsychiatric disorders [24]. The establishment of a connection between TSC1/TSC2 mutations and mTOR led to the clinical use of drugs known as mTOR inhibitors: sirolimus and everolimus. These are becoming an increasingly interesting tool in the management of TSC-associated symptoms and epileptogenesis [23, 25]. It has been demonstrated that mTOR inhibitors can be used in the treatment of many features of TSC, including subependymal giant cell astrocytomas (SEGA), renal angiomyolipomas (AML), lymphangioleiomyomatosis (LAM), and skin lesions [26–29]. Moreover, EXIST-3, a recent prospective, randomised, multicentre, placebo-controlled study, established that everolimus can be used as adjunctive therapy for the treatment of refractory seizures associated with TSC [30]. Everolimus reduces seizure frequency in a dose-dependent manner with a tolerable safety profile in TSC patients with refractory epilepsy [30]. The odds for response in patients treated with everolimus were 2.2–3.9 times higher than with a placebo [30]. Furthermore, a positive effect of everolimus has been observed in a variety of seizure types [30].

In conclusion, we feel that the mTOR pathway represents a great opportunity for future novel antiepileptogenic drugs. Moreover, another benefit of the use of mTOR inhibitors in TSC is the possibility of simultaneously improving not only one manifestation, e.g. SEGA or seizures, but also other TSC symptoms. The currently available findings regarding mTOR inhibitors, both clinical and pre-clinical, are intriguing and highly supportive of future experiments.

Currently, TSC is considered to be one of the best models for prospective studies of epileptogenesis in humans due to a homogenous group of patients, the possibility of a diagnosis before seizures, and the possibility of early (before clinical seizures) and easy detection of epileptogenesis based on ictal discharges on EEG.

Hence, at present there are two large, multicentre studies on epilepsy prevention in TSC in Europe and the US ongoing: EPISTOP (ClinicalTrials.gov Identifier: NCT02098759) (www.epistop.eu) and PREVENT (ClinicalTrials.gov Identifier:

NCT02849457). The EPISTOP project is focused not only on the prevention of epilepsy but also on the identification of the clinical and molecular biomarkers of epileptogenesis in humans. The project ended in April 2019 and the results of EPISTOP may shed new light on the management and prevention of epilepsy in humans.

Undoubtedly, the prevention of epilepsy is a serious challenge. However, prevention is possible, and it has been proved that preventive treatment may be particularly effective and important in epileptic encephalopathies such as TSC and SWS, reducing not only seizures but also their comorbidities [31]. Future studies using predictive biomarkers will demonstrate the extent to which this may be useful in other types of seizures, and in adult patients.

Acknowledgments and funding

This study was in part supported by the 7th Framework Programme of the European Commission within the Large-scale Integrating Project EPISTOP (Proposal No: 602391–2; Proposal title: 'Long term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex'; www.EPISTOP.eu), the Polish Ministerial Funds for Science (years 2014–2018) for the implementation of international co-financed projects, and the grant EPIMARKER of the Polish

National Centre for Research and Development No STRATEGMED3/306306/4/2016.

Conflict of interest: *The authors declare no conflict of interest.*

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