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Stop the Lights—Turning Off the Electricity in Tuberous Sclerosis

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Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial

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Objective: Epilepsy develops in 70 to 90% of children with tuberous sclerosis complex (TSC) and is often resistant to medication. Recently, the concept of preventive antiepileptic treatment to modify the natural history of epilepsy has been proposed. EPISTOP was a clinical trial designed to compare preventive versus conventional antiepileptic treatment in TSC infants. Methods: In this multicenter study, 94 infants with TSC without seizure history were followed with monthly video electroencephalography (EEG), and received vigabatrin either as conventional antiepileptic treatment, started after the first electrographic or clinical seizure, or preventively when epileptiform EEG activity before seizures was detected. At 6 sites, subjects were randomly allocated to treatment in a 1:1 ratio in a randomized controlled trial (RCT). At 4 sites, treatment allocation was fixed; this was denoted an open-label trial (OLT). Subjects were followed until 2 years of age. The primary endpoint was the time to first clinical seizure. Results: In 54 subjects, epileptiform EEG abnormalities were identified before seizures. Twenty-seven were included in the RCT and 27 in the OLT. The time to the first clinical seizure was significantly longer with preventive than conventional treatment [RCT: 364 days (95% confidence interval [CI] = 223-535) vs 124 days (95% CI = 33-149); OLT: 426 days (95% CI = 258-628) vs 106 days (95% CI = 11-149)]. At 24 months, our pooled analysis showed preventive treatment reduced the risk of clinical seizures (odds ratio [OR] = 0.21, $P = 0.032$), drug-resistant epilepsy (OR = 0.23, $P = 0.022$), and infantile spasms (OR = 0, $P < 0.001$). No adverse events related to preventive treatment were noted. Interpretation: Preventive treatment with vigabatrin was safe and modified the natural history of seizures in TSC, reducing the risk and severity of epilepsy.

Commentary

Our efforts to treat epilepsy are reactionary; we wait for seizures to occur, even waiting longer to initiate anti-seizure medication. Non-pharmacological options are even a more distant sight on the horizon. Can we turn off the electricity at or close to source? Therapeutic efforts have long sought the prevention of epileptogenic foci, considered to be a major unmet need by the epilepsy community, and recently by the World Health Organization.[1,2]

A careful distinction needs to be made between anti-epileptic (that is, to prevent the development of epileptogenicity) and anti-seizure medication. This is outlined in recent ILAE recommendations on the use of ASM (anti-seizure medication) rather than AED (anti-epileptic drugs) in our day-to-day lexicon.[3]

Thus, trials of preventative treatments are most welcome and critically important in moving the field forward beyond symptomatic treatment of seizures.

To date, prevention efforts have focused on acute brain injury, with limited success, no positive phase 3 randomized controlled trials,[4] and the incidence of epilepsy over time stable or increasing, rather than decreasing.[5]

Tuberous sclerosis complex (TSC) is a good example of a condition that is amenable to the development of a preventative therapy. TSC is a genetic syndrome usually caused by mutations in the TSC1 or TSC2 gene leading to excessive activation of the mTOR signalling pathway. TSC can be diagnosed *early*, often in utero by fetal echocardiography or MRI brain. Epilepsy and neurodevelopmental disorders are common.

Subtle seizures such as focal tonic or clonic seizures, often missed by parents, can occur in the neonatal period, and these can evolve into drug-refractory epilepsy in the first few months of life.[6]

A window may exist to act before the development of drug-refractory epilepsy or infantile spasms, where we could prevent or limit the epilepsy, and perhaps improve neurodevelopmental outcomes.

Prior studies have shown that earlier seizure onset, and infantile spasms led to worse neurodevelopmental outcomes and higher rates of autistic spectrum behaviour in TSC.[7]

A preventative effort needs a reliable biomarker and an effective intervention; Vigabatrin is first line therapy for TSC-associated spasms or seizures in the first year of life. Vigabatrin increases GABA levels, but could also inhibit mTOR activation

in animal studies, so may have an additional role in epileptogenesis.[8] There is data to support pre-symptomatic use of Vigabatrin preventively or in the presence of epileptiform changes on EEG. EEG in this case is a biomarker for the development of epilepsy; epileptiform discharges on EEG had a 100% positive predictive value for the development of epilepsy in a series of 40 patients with TSC.[9]

A prospective nonrandomized study of preventative Vigabatrin when electrographic abnormalities were detected, followed patients to age 5 years. Median IQ was 94 for the preventive group and 46 for the standard treatment group. Fifty percent of patients in the preventive group never had a seizure vs 5% in the standard group.[10]

In the work highlighted here, Kotulska and the EPISTOP investigators evaluated whether preventative treatment with Vigabatrin at detection of interictal epileptiform activity on EEG (EA) vs conventional use after the occurrence of clinical or EEG seizures would modify the natural course of the epilepsy in TSC. Patients had definite TSC and were under 4 months of age, and must have had no prior clinical seizures or epileptiform discharges on baseline EEG.

The primary outcome was the time from birth to the first clinical seizure, with evaluation up to the age of 2 years. Patients were randomized or allocated treatment at detection of EA (defined as unifocal discharges for >10% of the recording, multifocal discharges or generalized epileptiform activity). Study visits included a 1 hour awake and sleep EEG and were every 4 weeks if <6 months, every 6 weeks for 6-12 months, every 8 weeks if over 12 months.

Both treatments consisted of Vigabatrin 100-150 mg/kg/day. Infants who did not develop clinical seizures or EA did not receive any treatment. In patients on preventative treatment with no seizures by 2 years, the Vigabatrin was tapered off.

Approval by the ethics board was not received at 4 of 10 sites. At these sites, an open label trial format was used with placement into preventative or conventional groups based on local clinical practice.

Fifty-four patients, were allocated to either preventative or conventional treatment, either as part of the randomized controlled trial (RCT) (13 vs 14 patients) or open label study (OL) (12 vs 15 patients). Mean age at enrolment was between 36-43 days. Secondary endpoints at 2 years of age were the proportion of patients with clinical seizures, drug-resistant epilepsy (failure of 2 ASM), history of infantile spasms or EEG hypsarrhythmia, any EEG abnormalities, autistic features, and neurodevelopmental delay.

In a pooled analysis (RCT and OL) of the primary outcome, the median time to clinical seizure onset was day 614 in the preventative group and 124 for the conventional group (the same result was obtained in the RCT group alone). The median time from EEG epileptiform activity to any seizure (clinical or electrographic) was 561 days vs 61 days.

Secondary outcome findings included a lower median proportion of days with seizures (8 vs 43.5%), and lower frequency of drug resistant epilepsy (28 vs 64%). No infantile spasms occurred in the preventative group, while 10 occurred in the conservative arm. No significant differences were observed in neurodevelopmental delay, and autism. There were no adverse events.

As the authors mention, there are 2 interventions in this trial– the use of frequent EEG to detect EA as a biomarker for epileptogenicity, and the early preventative use of Vigabatrin. This inclusion of both biomarkers and preventative treatment has been identified as a way of accelerating progress in epilepsy prevention trials.[4]

The trial showed that preventative Vigabatrin is safe, and the positive primary outcome showed promising efficacy at changing the natural course of epilepsy in TSC. However, numbers were low, and secondary outcomes for neurodevelopmental measures were not met. Other secondary outcomes were only significant in the pooled analysis of randomized and open label patients. While these results are confined to TSC, it would be intriguing to apply early intervention to other early onset epilepsies.

Some inevitable bias exists in part due to the inclusion of open-label patients in a pooled analysis. Blinding in the RCT was maintained by the local EEG reader sending the EEG for central study review, and a subsequent decision on randomisation, without the knowledge of the primary physician of the EEG results. Although there was no sham treatment, the treating physicians did not know whether Vigabatrin was started due to EA or EEG seizures. This, however, remains a potential source of bias. In fact, in some cases 'immediate action' was taken locally on the EEG, and where the local interpretation was discordant with central review, these 7 patients were excluded. No intention to treat analysis was done, although only 4 patients out of 54 dropped out after assignment to the RCT and OL groups.

The authors must be commended for completing a clinical trial in a difficult scenario, where parents have to process that their infant has been diagnosed with a chronic genetic neurological condition. Out of 101 patients screened, the 2 arms of the randomized portion of the trial had 13 vs 14 participants, highlighting the difficulties the trial faced in recruitment.

EEG fulfils the role of a candidate biomarker by being able to detect changes early, predict the development of epilepsy, and follow it over time.[4] However, EEG may only be done practically at intervals of a few weeks, so may miss an earlier onset of EA. Other potentially useful biomarkers include blood biomarkers such as microRNA, PET ligand imaging, fMRI and transcranial magnetic stimulation.[11] With emerging understanding of the natural course of epilepsy in TSC, the importance of early and follow-up EEG to study the 'pre-epileptogenic brain' in TSC seems clear. How many patients have epileptiform changes on EEG before the onset of seizures in other epilepsies? Wider use of EEG in at-risk groups for this reason would have to justify resource allocation of EEG and clinico-economic benefit. Application of EEG machine learning and quantitative algorithms, which have shown promise for detecting pre-ictal seizure activity in the acute or inpatient setting, could be applied to interictal EEG in the predictive analysis of epilepsy.[12]

How can we clearly differentiate between an anti-seizure effect and an anti-epileptic effect? Why did the improved seizure outcomes not translate into developmental benefits?

We are perhaps more likely to find an anti-seizure effect than a more complex downstream effect on neurodevelopment, which is a result of more complex processes, partly independent of the epilepsy in the TSC brain.[13] Potentially a drug washout/discontinuation and longer follow-up is needed to separate these effects out. However, this study is an important step in the pathway of preventing drug resistant epilepsy, and infantile spasms, and ultimately improving neurodevelopmental outcomes.

Targeted treatment in TSC such as rapamycin inhibitors (although currently approved for only >2 years of age), and surgical removal of epileptogenic tubers can also improve outcomes. Differences between genetic/developmental epilepsies and the post-acute injury epilepsies, will need ongoing translational efforts at understanding the pathophysiology of epileptogenesis.[14]

Collaborative efforts such as the EpiBioS4Rx consortium for post-traumatic epilepsy and EPITARGET will help achieve this.[14,15]

We await the results of the PREVeNT trial (preventing epilepsy using Vigabatrin in infants with tuberous sclerosis complex, https://clinicaltrials.gov/ct2/show/NCT02849457) due to be completed in 2022. Infants with TSC and no evidence of epilepsy under 6 months will be randomized to Vigabatrin vs placebo. Their primary outcome is focused on neurodevelopment with cognitive assessment scores at 24 months.

In the meantime, EEG surveillance for EA and seizures, and caregiver and parent education to recognise early or subtle seizures should facilitate early referral and treatment for TSC-associated epilepsy.

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