

## Uncommon Treatable Genetic Epileptic Encephalopathies

Epileptic encephalopathies refers to a group of disorders where cognitive and behavioral deterioration occurs as a direct consequence of frequent seizures and epileptiform discharge, and is not solely due to the underlying cause of the seizures. Most of them have a poor motor and cognitive prognosis [1]. Few of these are treatable; *e.g.*, pyridoxine dependency, folinic acid responsive seizures, biotinidase deficiency, glucose transporter-1 deficiency syndrome and creatine deficiency syndrome. Most recommendations advise use of these drugs/strategies for managing these children where obvious cause like perinatal insult is not evident [1,2].

In this group of epileptic encephalopathies, broad spectrum anti-epileptic drugs such as sodium valproate (once inborn errors of metabolism are ruled out), phenobarbitone, benzodiazepines and levetiracetam are preferred. At the same time, we tend to avoid sodium channel blockers like phenytoin and carbamazepine among these group of patients. However, there are conditions like *KCNQ2* encephalopathy and *SCN2A* encephalopathy that present with refractory focal and generalized clonic/ tonic seizures starting in the first few weeks of life along with developmental arrest, and may have burst suppression pattern on EEG [3,4]. Mutations in these genes usually present as benign familial neonatal seizures which are self limiting or get easily controlled with one anti-epileptic drug but some children may present with features of an epileptic encephalopathy. These conditions respond dramatically to sodium channel blockers like phenytoin, carbamazepine, lacosamide, mexilitine and lignocaine [3-5]. Owing to apprehension of apparent clinical worsening, there is trend towards avoiding phenytoin among children with epileptic encephalopathy and there is good chance that we miss many of cases of treatable *KCNQ2* and *SCN2A* encephalopathies.

We managed three infants with epileptic encephalopathy with normal neuroimaging who had seizures (10-50 per day) starting in the first month of life. These babies had failed trial of pyridoxine, pyridoxal phosphate, steroids, folinic acid, ketogenic diet and anti-epileptic drugs like levetiracetam, clonazepam,

phenobarbitone, topiramate, and sodium valproate. Phenytoin dramatically controlled the seizures and reversed the encephalopathy. EEG also normalized in two weeks. Next generation sequencing (NGS) for epilepsy panel revealed pathogenic mutation in *KCNQ2* gene (autosomal dominant) in two babies [heterozygous missense in exon 15 at c.1657C>T (p.Arg553Trp) in one and in exon 3 at c.440C>A (p.Ala147Asp) in the other baby, and *SCN2A* (autosomal dominant) in one [heterozygous missense in exon 7 at c.794T>C (p.Ile265Thr)] baby. The babies with *KCNQ2* genes had a likely pathogenic mutation and hence parental testing was not advised, whereas the results of parental testing of the child with *SCN2A* mutation which was a variant of unknown significance is awaited. The follow-up of these babies for 6 months showed good control of seizures with occasional fever-triggered seizures and near normal development.

In developing countries like India, epileptic encephalopathies secondary to perinatal insults are common and in these conditions the diagnosis is suggested by history and imaging findings. Here we avoid sodium channel blockers like phenytoin and carbamazepine as they aggravate myoclonic seizures and spasms seen in these children. However, in epileptic encephalopathies without an obvious cause, therapeutic trial with pyridoxine, pyridoxal phosphate, biotin, and folinic acid is always warranted pending the results of next generation sequencing. Based on our observations, we propose to add sodium channel blockers to this armamentarium of potential therapeutic drugs, pending the genetic testing results.

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## Epidemiology and Demographic Features of Dengue Infection in Children

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We read with interest the study by Mistry, *et al*. [1] published recently in *Indian Pediatrics*, and have few comments:

1. In Methods, it is not clearly written whether sample database is from outpatient department or inpatient department; or from single institute or multiple institutes.
2. Authors excluded samples with evidence of co-infections like malaria, typhoid or any co-morbid diseases. As the study was primarily concerned regarding the epidemiology of dengue infection, there was no need to exclude other infections or co-morbid illness. In fact this could have led to less number of cases of dengue than expected. Including co-infections could have added another analytical point about magnitude of co-infections in dengue, which could have bearing on management.
3. In the result section, authors have mentioned dengue positivity rate in percentages (positivity ranged from 44.1% in year 2013, 25.8% in 2015 to 16.1% in year 2017), but drainage area and population mass is not clearly defined. Authors should have mentioned the sensitivity and specificity of the test kits either from the previous studies or data from the manufacturers.

It is noteworthy that despite seasonal trends, patient should always be investigated for dengue when there is high index of clinical suspicion.

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### AUTHOR'S REPLY

We thank you for reading our article and raising some queries. Following is our response:

1. It is mentioned that the microbiology department is one of the sentinel surveillance center under NVBDCP. It included all samples received from OPD, IPD, and from multiple hospitals.
2. Based on our primary objective, we included only samples positive for dengue and excluded others. Our objective was not to assess co-infections with dengue.
3. We included only those cases who were diagnosed by IgM or NS1 Antigen test which are diagnostic tests and not the screening test. Thus, sensitivity and specificity was not mentioned.

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