KCNQ2 Encephalopathy and Effect of Early Treatment on the Clinical Phenotype

Sir,

Mutations in the *KCNQ2* gene that encodes for a voltage-dependent potassium channel subunit 7.2 (k_v 7.2) are associated with a wide clinical spectrum ranging from milder variants such as benign familial neonatal seizures to a severe phenotype of neonatal-onset developmental and epileptic encephalopathy (DEE).[1] The severe end of the spectrum, which is associated with either suppression burst pattern or multifocal epileptiform discharges on electroencephalography (EEG), is called *KCNQ2* encephalopathy. It is not clear from the literature whether it is the type of genetic mutation or it is the recurrent clinical and sub-clinical seizures before appropriate treatment is instituted that leads to the poor outcome.[2-5] If the latter statement is true, then early institution of appropriate anti-seizure medications in the form of sodium channel blockers (SCBs) can result in quick and good seizure control, thereby improving the neurodevelopmental outcome.

A retrospective chart review of all children with genetically confirmed *KCNQ2* encephalopathy (either pathogenic or likely pathogenic mutations) diagnosed over the last 4 years was done. The details of the age of onset of seizures, age at treatment with SCBs, age at final genetic diagnosis, EEG, neuroimaging findings, neurocognitive outcome and current status are shown in Table 1. All presented with neonatal seizures in the first week and the seizures continued beyond the neonatal period till SCB were prescribed. The EEG showed multifocal epileptiform discharges or suppression burst pattern, suggesting epileptic encephalopathy and neuroimaging in the early life was normal. Basic biochemical investigations, screening for neurometabolic disorders, and cerebrospinal fluid examination were normal in all. Only in case 2, there was history of neonatal seizures in the father and paternal uncle. Genetic diagnosis was reached very late in all except case 2, because of lack of availability of testing facilities in the beginning and later high cost of testing (after testing became available). Irrespective of the type of treatment taken, the seizure frequency diminished by 1–2 years of age, but the outcome was seriously influenced by the time of initiation of SCBs. In the two cases (cases 1 and 2) where the treatment was started in the neonatal period, the outcome (psychomotor and cognitive) was normal, and when there was delay by even a few months (cases 3 and 4), there was impairment of language milestones with either hyperactivity or autistic behaviour. In case 5, where the diagnosis was delayed by 7 years and the child was not given SCBs, along with language delay, the boy also had motor involvement in the form of mixed quadriparesis (spasticity with dystonia) severe enough to cause contractures and needing surgical intervention (tendon release). Repeat MRI of case 5 at 7-years of age showed a paucity of white matter with mild cerebral atrophy. In all children, after the initiation of SCBs such as phenytoin, oxcarbazepine and lacosamide, the seizures stopped but the language impairment and the motor involvement persisted. At follow-up, those with normal development had normal EEGs while those with sequelae had slow background activity and occasional spikes.

KCNQ2 encephalopathy is a type of DEE and can present as neonatal or infantile focal or generalised seizures with a predominant tonic component. They can also present as clonic, seizures or spasms (myoclonic jerks are rare). Though the seizures go into remission at a median age of 2 years, many children have moderate to severe cognitive impairment with motor manifestations in the form of dysphagia and hypertonia, which could be due to either spasticity and/or dystonia.[2,6] Many of them are associated with autistic spectrum disorder (ASD) and/or intellectual disability (ID).

Epilepsy, ASD and ID are now considered to be synaptopathies that are brain disorders that have arisen from synaptic dysfunction regardless of their pathophysiological origin.[7] *KCNQ2* gene causes dysfunction of potassium ion channels, and because they co-localise with sodium channels, it leads to increased excitatory neurotransmission. Features of ASD, ID and epileptic encephalopathy may result from an imbalance between excitatory and inhibitory signalling in different parts of the CNS. The imbalance between excitation and inhibition in neocortical areas has been proposed as a key process underlying ASD pathogenesis and increased excitation due to sodium channels can result in epilepsy.[7]

The variability in cognitive, language and motor outcomes associated with different *KCNQ2* variants makes it difficult to conclude if early seizure control can affect neurodevelopmental outcome.[4-6] While many have reported poor cognitive and

Table 1: Salient clinical, genetic diagnosis, neuroimaging and therapeutic response of children with KCNQ2 encephalopathy

	Case 1	Case 2	Case 3	Case 4	Case 5
Age of onset	5 days	Day 1 of life	Day 2 of life	Day 5 of life	Day 2 of life
Age at diagnosis	18 months	3 months	4 yr	5 yr	7 yr
Mutation analysis	Exon 3 c.440C>A (p.Ala147Asp) Heterozygous	Exon 15 Variant: c. 1657C>T (p. Arg553Trp) Heterozygous	Exon 4 c. 620G>A (p.Arg207Gln) Heterozygous	Exon 15 c. 1696G>A (p.Asp566Asn) Heterozygous	Exon 5 c. 788C>T (p.Thr263ile) Heterozygous
ACMG	Missense, LP	Missense, pathogenic	Missense, LP	Missense, LP	Missense, LP
Age of starting SCB	1 month	1.5 months	9 months	5 yr	7 yr
Seizure free since	1 month of age	2.5 months of age	On and off seizures when SCB withdrawn; Seizure free from 2 yr of age after SCB	5 yr	5 yr
Present age	2 yr 10 m	1 yr 8 m	4 yr 10 m	7.5 yr	7.5 yr
Development assessment	Normal (DASII)	Normal (DASII)	Delayed milestones, poor speech (Moderate ID-MISIC)	Speech delay (Moderate ID-MISIC)	Severe ID with mixed quadriparesis (MISIC)
MRI	Normal	Normal	Mild cerebral atrophy	Normal	Mild cerebral atrophy with paucity of white matter
EEG at presentation	Multifocal epileptiform discharges	Multifocal epileptiform discharges	Multifocal epileptiform discharges with suppression burst pattern	Multifocal epileptiform discharges seen	Multifocal epileptiform discharges with suppression burst pattern
Autistic/ADHD	No	No	Hyperactivity, Autistic behaviour, poor eye contact	Moderate ID with ADHD	Because of severe ID, ASD diagnosis could not be clearly done

ID-Intellectual disability, ADHD-Attention deficit hyperactivity disorder, EEG- Electroencephalography, ACMG-American college of Med genetics classification, SCB-Sodium channel blockers, LP-likely pathogenic, DASII-(Developmental assessment scale for Indian Infants) in children up to 3 years and MISIC-Malin's intelligence scale of Indian Chidren (>3 yrs)

motor outcome despite seizure control, few have mentioned that early seizure control results in better cognitive outcome.[2,3,5,6] SCB like phenytoin, carbamazepine and lacosamide are found to effectively control the seizures in *KCNQ2* encephalopathy by down-regulating the sodium channels that are modulated by the mutated potassium channels.[1,2,4,8] Patients who do not respond to phenytoin may respond to carbamazepine or lacosamide.

In the *KCNQ2* gene, mutations can cause haploinsufficiency (presents as benign familial or nonfamilial neonatal seizures), a more severe dominant-negative effect by a loss-of-function (presents as KCNQ2 DEE) or a gain-of-function (presents as neonatal encephalopathy with suppression burst pattern on EEG but without seizures, exaggerated and prolonged startle response with bilateral high amplitude myoclonic jerks without EEG correlate, hypoventilation with periodic breathing, epileptic spasms between 4–6 months and profound developmental impairment). This is important, as potassium-channel openers/activators can help in loss-of-function mutation cases but can worsen those with gain-of-function mutation.[9]

As genetic tests are not routinely done and even if done, the results take 4–6 weeks, there is a delay in the use of SCB. This delay in treatment with SCB can result in recurrent seizures, status epilepticus and excessive excitation in the neocortex, resulting in ASD and ID in children with *KCNQ2* encephalopathy as is evident in our cases 3–5. Many case series on *KCNQ2* encephalopathies have also shown that when SCBs were used early, the babies have only mild cognitive impairment.[2,4,5] Our cases 1 and 2, where the SCBs were used in the first 4–6 weeks, had near-normal developmental milestones at 2-years of age.

We suggest that a targeted therapeutic approach should be considered in the treatment of neonatal epilepsies. For those neonates with seizures not responding to routine line of management and that are not attributable to a specific cause and for whom a genetic aetiology is suspected, early trial of SCB (with careful observation for any worsening of seizures) should be considered pending the genetic results.[10]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Mahesh Kamate, Anuraag N. Reddy[1], Mayank Detroja[2]

Departments of Pediatric Neurology and In-Charge Child Development Clinic, and [1]Paediatrics, KAHER's J N Medical College, Belagavi, Karnataka State, [2]Department of Child Development Centre, KLES PK Hospital, Belagavi, Karnataka State, India

Address for correspondence: Dr. Mahesh Kamate,
Department of Paediatric Neurology, KAHER's J N Medical College, Belgaum,
Karnataka State - 590010, India.
E-mail: drmaheshkamate@gmail.com

References

1. Spagnoli C, Salerno GG, Iodice A, Frattini D, Pisani F, Fusco C. *KCNQ2* encephalopathy: A case due to a de novo deletion. Brain Dev 2018;40:65-8.
2. Pisano T, Numis AL, Heavin SB, Weckhuysen S, Angriman M, Suls A, *et al*. Early and effective treatment of *KCNQ2* encephalopathy. Epilepsia 2015;56:685-91.
3. Srivastava S, Sahin M. Autism spectrum disorder and epileptic encephalopathy: Common causes, many questions. J Neurodev Disord 2017;9:23-34.
4. Schubert-Bast S, Hofstetter P, Fischer D, Schloesser R, Ramantani G, Kieslich M. Sodium channel blockers in *KCNQ2*-encephalopathy: Lacosamide as a new treatment option. Seizure 2017;51:171-3.
5. Malerba F, Alberini G, Balagura G, Marchese F, Amadori E, Riva A, *et al*. Genotype-phenotype correlations in patients with de novo *KCNQ2* pathogenic variants. Neurol Genet 2020;6:e528.
6. Millichap JJ, Park KL, Tsuchida T, Ben-Zeev B, Carmant L, Flamini R, *et al*. *KCNQ2* encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. Neurol Genet 2016;2:e96.
7. Lepeta K, Lourenco MV, Schweitzer BC, Martino Adami PV, Banerjee P, Catuara-Solarz S, *et al*. Synaptopathies: Synaptic dysfunction in neurological disorders-A review from students to students. J Neurochem 2016;138:785-805.
8. Kuersten M, Tacke M, Gerstl L, Hoelz H, Stülpnagel CV, Borggraefe I. Antiepileptic therapy approaches in KCNQ2 related epilepsy: A systematic review. Eur J Med Genet 2020;63:103628.
9. Mulkey SB, Ben-Zeev B, Nicolai J, Carroll JL, Grønborg S, Jiang YH, *et al*. Neonatal nonepileptic myoclonus is a prominent clinical feature of KCNQ2 gain-of-function variants R201C and R201H. Epilepsia 2017;58:436-45.
10. Kamate M, Detroja M. Uncommon treatable genetic epileptic encephalopathies. Indian Pediatr 2019;56:427-8.

Submitted: 18-Apr-2021 **Revised:** 05-Jun-2021 **Accepted:** 18-Jul-2021
Published: 12-Jan-2022

DOI: 10.4103/aian.aian_335_21