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Case Report

Paediatrics Section

Early-Onset Epilepsy in Infancy Associated with Mutations in *KCNQ2* and *SCN8A*: A Report of Two Cases

AYUSHI RAJESHBHAI AGRAVAT[1], RISHIT MAHESHBHAI MAKADIA[2], HALAK HASMUKHBHAI CHAUHAN[3], PANKTI DHAIVAT DESAI[4], SUNIL CHANDRASEN CHAND[5]

ABSTRACT

Neonatal seizures are most commonly attributed to hypoxic-ischaemic injury, metabolic abnormalities, or central nervous system infections; however, an increasing proportion of cases are recognised to have an underlying genetic aetiology, particularly when routine investigations are non-contributory. Present report is of two neonates with early-onset seizures caused by distinct monogenic channelopathies who demonstrated markedly divergent clinical courses and outcomes. The first case was a near-term female neonate who presented on day 8 of life with recurrent tonic seizures and a significant family history of unexplained infantile death in a sibling. Comprehensive evaluation revealed no metabolic or structural abnormalities. Whole-Exome Sequencing (WES) identified a heterozygous pathogenic loss-of-function variant in the *KCNQ2* gene. Seizures were controlled with phenobarbital monotherapy, and the infant remained seizure-free with age-appropriate neurodevelopment at 12 months of follow-up. The second case was a term male neonate who presented on day 11 of life with focal autonomic seizure clusters. Magnetic Resonance Imaging (MRI) brain demonstrated non-specific pachymeningeal enhancement. Despite treatment with five antiepileptic drugs (AEDs), seizures remained pharmacoresistant. Genetic analysis revealed a heterozygous variant of uncertain significance (VUS) in the *SCN8A* gene (c.1157C>A; p.Thr386Lys) and an additional heterozygous *SLC6A1* variant (c.582G>T; p.Glu194Asp). By four months of age, the infant exhibited profound global developmental delay. These cases illustrate contrasting clinical trajectories in neonatal channelopathies with similar ages at seizure onset.

Keywords: Developmental and epileptic encephalopathy, Genotype-phenotype correlation, Neonatal epilepsy, Pharmacoresistant epilepsy, Voltage-gated ion channels

CASE REPORT

Case 1

A near-term female infant (36 weeks gestation, 2.4 kg) was born via emergency Lower Segment Caesarean Section (LSCS) [Table/Fig-1]. On the eighth day of life, following an uneventful early phase, she presented with recurrent, unprovoked tonic seizures characterised by bilateral limb extension occurring 5-10 times per day. There was a significant family history of an elder sibling who died at one year of age following a history of seizures. Investigations including arterial blood gas, serum ammonia, lactate, electrolytes, and metabolic screening Tandem Mass Spectrometry (TMS) and Gas Chromatography-Mass Spectrometry (GCMS) were within normal limits. Genetic testing (WES) was pursued due to early-onset seizures, normal metabolic and neuroimaging evaluation, and a significant family history of epilepsy-related mortality. WES identified a heterozygous pathogenic loss-of-function variant in exon 4 of the *KCNQ2* gene [Table/Fig-2]. Neuroimaging via MRI was also normal [Table/Fig-3]. Following this diagnosis, seizures were successfully controlled with Antiepileptic drug (AED) monotherapy, and the infant demonstrated normal milestones at 12-month follow-up.

Parameter	Case 1 (*KCNQ2*)	Case 2 (*SCN8A*)
Gestation/Birth weight	36 weeks/2.4 kg	39 weeks/3.1 kg
Early phase	Uneventful (First 7 days)	Uneventful (First 10 days)
Sibling history	Positive (Sibling death at 1 yr)	Negative
Metabolic workup	Normal (TMS, GCMS, Ammonia)	Normal (TMS, GCMS, Ammonia)
Nutrition management	Enteral nutrition (Day 2)	Enteral nutrition (Day 5)
MRI findings	Normal	Pachymeningeal enhancement
Molecular mechanism	Loss-of-function (K^+ channel)	*SCN8A* variant (VUS)
Seizure control	Controlled with AED	Pharmacoresistant (5 AEDs)
Follow-up outcome	Normal development (12 m)	Global delay (4 m)

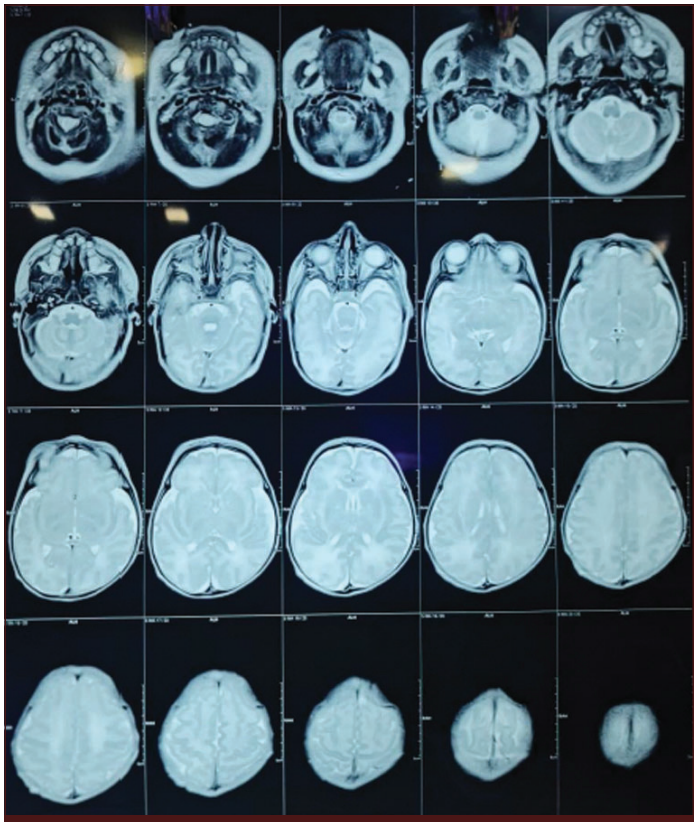
[Table/Fig-1]: Clinical and metabolic comparison of perinatal, imaging, and genetic outcomes in neonates with *KCNQ2* and *SCN8A* mutations.

Case 2

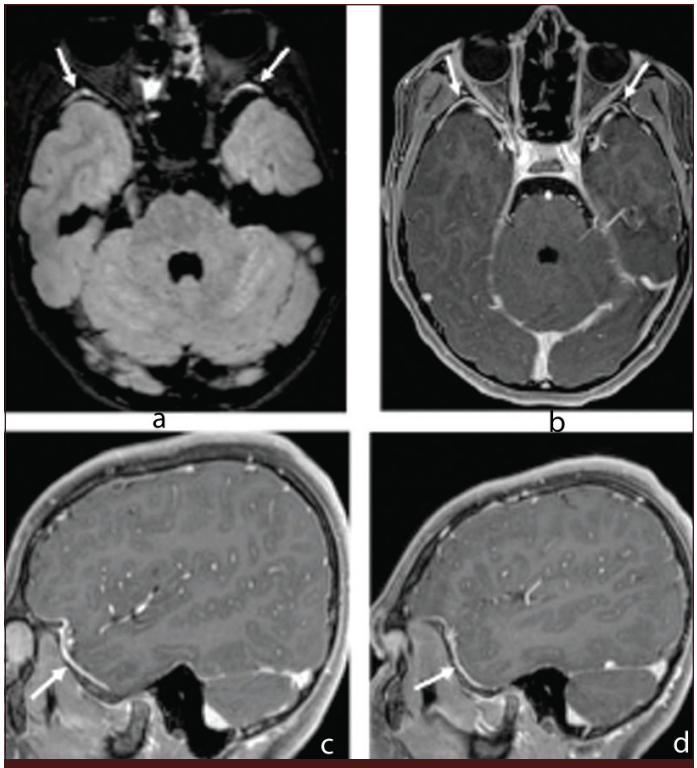
A full-term male (39 weeks gestation, 3.1 kg) presented on the 11th day of life with clusters of focal autonomic seizures involving eye deviation, apnoea, and desaturation. Baseline biochemical and metabolic investigations were normal. Seizures remained extremely pharmacoresistant despite the sequential use of five AEDs. There were no epileptic spasms or age-specific clinical features suggestive of West syndrome during the period of observation. Genetic testing was done in view of early-onset seizures with extreme pharmacoresistance despite appropriate antiseizure therapy. Genetic analysis identified a heterozygous *SCN8A* variant (c.1157C>A; p.Thr386Lys) and an additional heterozygous *SLC6A1* variant (c.582G>T; p.Glu194Asp), both classified as Variants of Uncertain Significance (VUS) [Table/Fig-4]. Despite aggressive polytherapy, the patient exhibited profound global developmental delay and axial hypotonia by four months of age. Brain MRI demonstrated incidental non specific pachymeningeal enhancement without evidence of structural malformation, a finding that was initially misleading [Table/Fig-5].

Gene	Genomic location	Zygosity	Classification
KCNQ2	Exon 4	Heterozygous	Pathogenic
Mitochondrial panel	N/A	N/A	Negative

[Table/Fig-2]: Summary of pathogenic genetic variants identified via whole exome sequencing.
N/A: Not applicable.



[Table/Fig-3]: Magnetic Resonance Imaging (MRI) of Case 1 (*KCNQ2*-related epilepsy). The images demonstrate normal sulcation and gyration patterns for gestational age. There is no evidence of hypoxic-ischaemic injury, intracranial haemorrhage, or structural malformations. The grey-white matter differentiation is well-preserved, consistent with the benign clinical trajectory of *KCNQ2* loss-of-function mutation.



[Table/Fig-5]: Magnetic Resonance Imaging (MRI) of Case 2 (*SCN8A*-related Epilepsy). The images demonstrate prominent pachymeningeal thickening and enhancement (white arrows), acting as a diagnostic 'red herring.' No structural malformations, cortical migration defects, or restricted diffusion were noted, highlighting that in genetic channelopathies such as *SCN8A*, neuroimaging abnormalities may be incidental and do not necessarily correlate with clinical severity.

which regulate neuronal membrane excitability. Pathogenic variants in *KCNQ2* have been described across a phenotypic spectrum ranging from self-limited familial neonatal epilepsy to severe neonatal-onset developmental and epileptic encephalopathy [3]. Foundational work by Singh NA et al., first identified *KCNQ2* mutations in benign familial neonatal seizures, establishing potassium channel dysfunction as a mechanism for neonatal epilepsy [4]. Subsequent cohort studies have demonstrated that loss-of-function variants

Gene (Transcript)	Exon	Variant (HGVS)	Zygosity	OMIM Disease	Inheritance	ACMG Class
SCN8A (ENST00000627620.5)	10	c.1157C>A / p.Thr386Lys	Het	DEE13 (#614558) / BFIS-5 (#617080)	AD	VUS (PM2)
SLC6A1 (ENST00000287766.10)	7	c.582G>T / p.Glu194Asp	Het	MAE (#616421)	AD	VUS (PM2, PP3)

[Table/Fig-4]: Detailed characterisation of single nucleotide variants and 'Dual-Hit' genotypes in case 2.
Het: Heterozygous; AD: Autosomal dominant; DEE13: Developmental and epileptic encephalopathy 13; BFIS-5: Benign familial infantile seizures type 5; MAE: Myoclonic-atonic epilepsy; VUS: Variant of uncertain significance
All genetic variant nomenclature has been corrected to HGVS-compliant format and aligned consistently across text and tables.

DISCUSSION

Neonatal seizures represent a significant diagnostic challenge, with causes ranging from hypoxic–ischaemic injury and infection to metabolic and structural abnormalities. However, an increasing proportion of early-onset seizures are now attributed to monogenic aetiologies, particularly ion channelopathies, when routine investigations are unrevealing [1]. Prospective population-based studies have demonstrated that single-gene epilepsies account for a substantial proportion of childhood-onset epilepsy, with an estimated incidence of approximately 1 per 2,000 live births [2]. Advances in next-generation sequencing have markedly improved recognition of neonatal developmental and epileptic encephalopathies.

Among potassium channelopathies, *KCNQ2*-related disorders represent a well-established cause of neonatal epilepsy. *KCNQ2* encodes the Kv7.2 subunit of voltage-gated potassium channels, are frequently associated with early seizure onset and favourable neurodevelopmental outcomes, particularly when seizures respond promptly to antiseizure therapy [3,5].

In Case 1, early-onset tonic seizures, absence of metabolic or structural abnormalities, and a positive family history were consistent with the classical *KCNQ2* self-limited phenotype. The favourable seizure control with phenobarbital monotherapy and normal neurodevelopment at 12 months parallel observations from multicentre cohorts demonstrating good prognosis in non encephalopathic *KCNQ2* variants [3,5]. These findings reinforce the importance of early genetic diagnosis in guiding prognostication and preventing unnecessary therapeutic escalation.

In contrast, *SCN8A*-related disorders are typically associated with more severe phenotypes. *SCN8A* encodes the Nav1.6 voltage-gated sodium channel, critical for action potential initiation and

propagation. Pathogenic variants often result in gain-of-function effects, leading to neuronal hyperexcitability and pharmacoresistant epilepsy [6-9]. Large genotype-phenotype correlation studies have demonstrated that *SCN8A*-related developmental and epileptic encephalopathy commonly presents within the first six months of life and is frequently associated with significant developmental impairment and treatment resistance [6,9]. International consensus statements and GeneReviews summaries similarly emphasise early pharmacoresistance and adverse neurodevelopmental outcomes in affected individuals [6,10].

Case 2 demonstrated seizure onset in the neonatal period, failure of five antiseizure medications, and early global developmental delay, consistent with the severe end of the *SCN8A* phenotypic spectrum described in published cohorts [6,9]. Notably, brain MRI demonstrated non specific pachymeningeal enhancement without structural malformation. Neuroimaging abnormalities in genetic epilepsies may be incidental and potentially misleading, acting as a diagnostic "red herring," particularly when infection and inflammation have been excluded. This underscores the need for early genetic evaluation when seizures are pharmacoresistant and metabolic studies are normal.

An additional complexity in Case 2 was the presence of a heterozygous *SLC6A1* variant. *SLC6A1* encodes the GABA transporter-1 (GAT-1), and pathogenic variants have been associated with developmental delay, epilepsy, hypotonia, and neurobehavioural impairment [11]. Although both *SCN8A* and *SLC6A1* variants were classified as variants of uncertain significance, the co-existence of two variants affecting excitatory and inhibitory pathways raises the possibility of oligogenic contribution. Emerging literature suggests that dual-variant or "multiple-hit` genetic mechanisms may modulate phenotypic severity in developmental epilepsies [12]. While functional validation was not available in index case, the extreme pharmacoresistance observed may reflect cumulative disruption of neuronal excitability.

The direct comparison of these two neonates highlights the marked heterogeneity of neonatal channelopathies. As summarised in [Table/Fig-1], both infants presented within the second week of life and had normal metabolic evaluations; however, their clinical trajectories diverged substantially. Case 1 followed a self-limited course consistent with milder *KCNQ2* phenotypes, whereas Case 2 demonstrated early pharmacoresistance and developmental impairment characteristic of severe *SCN8A*-related encephalopathy.

CONCLUSION(S)

The present report demonstrated the heterogeneous clinical spectrum of neonatal-onset epilepsy associated with channelopathies. Despite a similar age at seizure onset, one infant exhibited a self-limited course in the presence of a positive family history and favourable treatment response, while the other developed early pharmacoresistance with progressive developmental impairment. These contrasting trajectories highlight the importance of correlating seizure characteristics, treatment response, family history, and neurodevelopmental progression when evaluating neonatal seizures with otherwise non-specific initial investigations.

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PARTICULARS OF CONTRIBUTORS:

1. Resident Doctor, Department of Paediatrics, Narendra Modi Medical College, Ahmedabad, Gujarat, India.
2. Resident Doctor, Department of Paediatrics, Narendra Modi Medical College, Ahmedabad, Gujarat, India.
3. Assistant Professor, Department of Paediatrics, Narendra Modi Medical College, Ahmedabad, Gujarat, India.
4. Professor, Department of Paediatrics, Narendra Modi Medical College, Ahmedabad, Gujarat, India.
5. Associate Professor, Department of Paediatrics, Narendra Modi Medical College, Ahmedabad, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Ayushi Rajeshbhai Agravat,
Room No. 1012, PG Girls Hostel, Narendra Modi Medical College,
Ahmedabad-380008, Gujarat, India.
E-mail: ayushiagravat4@gmail.com

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