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Case Series

Pharmacogenetic based precision therapy in childhood epilepsy: a case series

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ABSTRACT

Childhood epilepsy poses a significant burden for parents as well as healthcare systems. Drug refractory epilepsy (DRE) is predominantly caused by structural brain lesions or gene mutations affecting ion channels or neurotransmitter function affecting the brain networks. Precision medicine in childhood epilepsies has revolutionised the approach to children with DRE/DEE by tailoring medications based on clinical and molecular aspects. We present a case series of four paediatric patients with drug-resistant epilepsy who demonstrated inadequate seizure control with conventional antiseizure medications but showed significant clinical improvement following precision therapy guided by proposed mechanisms based on the gene defect.

Keywords: Precision medicine, Genetic epilepsy, Epileptic encephalopathy, Pharmacogenomics

INTRODUCTION

Seizures in childhood represent the most common presenting neurological complaint. Drug refractory seizures are defined as 'failure to achieve control of seizures on two appropriately chosen anti-seizure medications at appropriate dose.[1]

Genetic epilepsies comprise a heterogeneous group of seizure disorders caused by pathogenic variants in genes essential for normal brain function. These genes commonly encode ion channels, neurotransmitter receptors, synaptic proteins, and components of neuronal development pathways.[2] Historically, management has relied on empiric trials of broad-spectrum antiseizure medications aimed at symptom control rather than addressing the underlying molecular pathology. Many patients with genetic epilepsies experience inadequate seizure control despite polytherapy, leading to significant morbidity including cognitive impairment, developmental regression, and reduced quality of life.

Recent advances in next-generation sequencing technologies and expanding knowledge of genotype-phenotype correlations have enabled a paradigm shift toward precision therapy.

This approach leverages molecular diagnosis to select treatments targeting specific pathogenic mechanisms. Several genetic epilepsy syndromes now have evidence-based precision treatment options, including SCN1A-related Dravet syndrome (cannabidiol, fenfluramine), KCNQ2 encephalopathy (retigabine), and ALDH7A1 deficiency (pyridoxine).[3]

As genetic testing becomes increasingly accessible and integrated into routine epilepsy care, precision therapy holds promise for transforming outcomes in children with genetic epilepsies.

We present four illustrative cases demonstrating how molecular diagnosis guided targeted therapeutic interventions, resulting in improved seizure control and developmental progress.

CASE SERIES

Case 1: STXBP1 related epilepsy

A 10-year-old girl, 1st born of non-consanguineous parents, presented with fever provoked seizures at the age of 13 months. Seizure semiology included generalised tonic clonic and myoclonic seizures. She continued to be encephalopathic in the form of extreme irritability with partial seizure control on Phenytoin and Valproate, hence was investigated further.

Electroencephalography demonstrated diffuse encephalopathy with bi-frontal discharges. MRI brain with MR spectroscopy was reported as normal and her metabolic and autoimmune workup was negative.

Whole exome sequencing did not reveal any pathogenic variants. However, chromosomal microarray analysis identified a 131 kilobase deletion at chromosome 16p11.2 encompassing the STX1B gene suggestive of monosomy. This was classified as de novo, autosomal dominant pathogenic variant and parental testing was negative.

Levetiracetam was added as precision therapy following the genetic reports- after which she improved and was seizure free. Withdrawal of drug after 2 years of seizure freedom was attempted twice-which resulted in breakthrough seizures on both the occasions. Hence, she has been continued at a low dose of 10 mg/kg/day. Developmentally, she continues to achieve milestones and excels in academics and martial arts.

Case 2: GRIN2D associated DEE

A 5-year-old girl, the second child of non-consanguineous parents was referred to our unit in view of refractory seizures and developmental delay. Family history was non-contributory.

There was a history of delayed cry at birth but no history of NICU stay or neonatal seizures. Seizure onset occurred at 2 years of age with tonic posturing of bilateral upper limbs with impaired awareness lasting 2-3 mins with a frequency of 1 episode every 2-3 months. Regression of developmental milestones was noted following seizure onset.

Electroencephalography revealed generalized polyspike-and-wave discharges with absence of age-appropriate background rhythm. MRI brain was reported as normal. Basic metabolic workup was normal. Prior to referral, she was treated with Sodium valproate, Clobazam, Levetiracetam, and Topiramate which provided only partial seizure control.

Suspecting DEE, genetic testing was done which identified a pathogenic autosomal dominant heterozygous missense mutation in exon 12 of GRIN2D gene. Precision therapy was started with Perampanel (an AMPA receptor antagonist) and Memantine (an NMDA receptor antagonist). This resulted in marked clinical improvement in terms of seizure control and developmental gains although EEG remained grossly abnormal. She was successfully weaned off other medications (sodium valproate, cannabidiol, topiramate, and clobazam).

Case 3: FRRS1L pathogenic mutation

A 7-year-old boy, 2nd born to third-degree consanguineous parents, presented with refractory seizures, global developmental delay and autistic traits for which he was undergoing rehabilitation therapies. Family history was otherwise unremarkable. Seizure onset occurred at 6 years of age with left focal seizures with impaired awareness precipitated by an upper respiratory tract illness. Soon his seizures became more frequent and refractory to multiple drugs – Sodium Valproate, Topiramate, Lacosamide and Clobazam.

Dysmorphic features were noted like relative macrocephaly, frontal bossing, arched eyebrows and coarse facial features. No neurocutaneous markers or organomegaly was noted. He was admitted with for status epilepticus at the age of 6 years, followed by prolonged twilight state where he was noted to be drowsy though responsive to stimuli.

Electroencephalography in the acute stage showed focal non convulsive status epilepticus originating from bilateral occipital regions with left predominance. MRI brain was normal. Initial treatment with pulse iv methylprednisolone worsened his seizures and irritability. Hence he was put on continuous midazolam infusion which was weaned off slowly.

Genetic testing identified a homozygous, autosomal recessive splice site mutation in FRRS1L (ferric-chelate reductase 1-like) and was classified as variant of unknown significance. Following genetic diagnosis, Perampanel was initiated based on its mechanism of action as an AMPA receptor antagonist. This resulted in excellent therapeutic response with seizure freedom for six months and notable improvements in cognition and speech.

However, parents stopped Perampanel after a few months which resulted in devastating seizures and regression of acquired milestones. Re-introduction of Perampenel at this stage showed some improvement but not as effective as seen initially.

Case 4: KCNC1 associated DEE

A 3-year-old boy presented at 22 months of age with refractory seizures. The onset of seizures was on day 25 of life with left focal clonic seizures and myoclonic seizures. There was h/o neonatal hypoglycemia on day 3 of life with documented heel prick blood glucose of 16 mg/dl. CSF study and sepsis screen was normal. EEG showed diffuse cerebral dysfunction with right centro-parietal

epileptogenic focus. MRI brain on Day 26 of life was reported as normal.

He presented to us with epileptic spasms at 5 months of age, for which he received Sodium valproate, Vigabatrin and high dose oral steroids. Genetic testing revealed a heterozygous autosomal dominant missense mutation of unknown significance in exon 3 of KCNC1 gene. Parental testing showed mother as a heterozygous carrier of same gene. Repeat MRI brain at 12 months of age showed linear hyperintensities in posterior mid brain and pons with mild hyperintensity in bilateral globus pallidi.

At 22 months of age, he started having increase in seizure frequency in the form of myoclonic jerks occurring in clusters and choreiform movements of bilateral upper limb. His EEG at that time was suggestive of hypsarrhythmia with bi-occipital spike and wave discharges. He was started on oral steroids and doses of existing anti-seizure medications (Sodium valproate and Vigabatrin) were optimised. Limited response was noted to treatment modifications.

After taking informed written consent from parents and doing necessary pre-medication screening (ECG and echocardiogram), child was started on low dose oral fluoxetine with steady increments every week to up to 0.5 mg/kg/day and monitoring of QTc interval every 6 weeks.

At 1 month follow up, spasms had reduced in frequency, he was fixing and following, holding head, laughing and uttering new monosyllables. He was less irritable. Fluoxetine was continued at same dose in addition to vigabatrin and clobazam was switched to clonazepam in view of predominant myoclonic jerks. He was successfully weaned off steroids, brivaracetam, lamotrigine and sodium valproate over a course of 6 months.

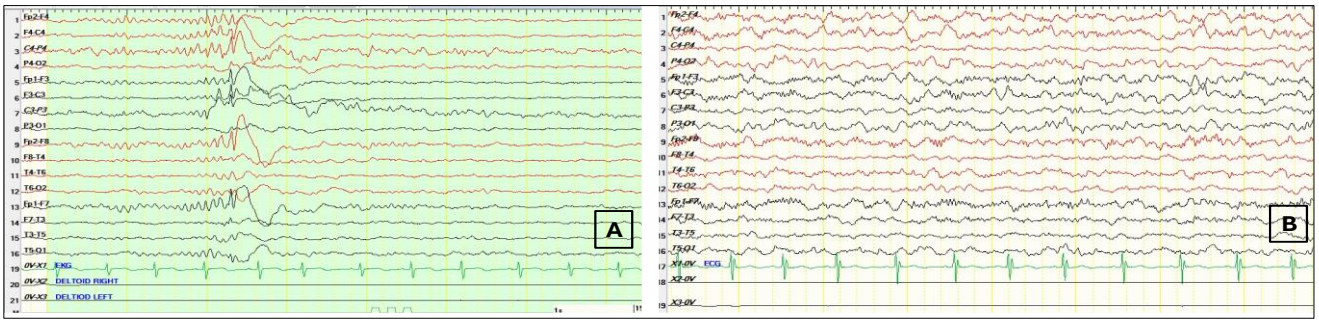

Figure 1: Case 1 (A) EEG of patient with STXBP1/CHD2 overlap showing frequent bi-frontal epileptiform discharges with predominant delta background suggestive of encephalopathy, and (B) following treatment with Levetiracetam, there is marked improvement of background activity with resolution of discharges.

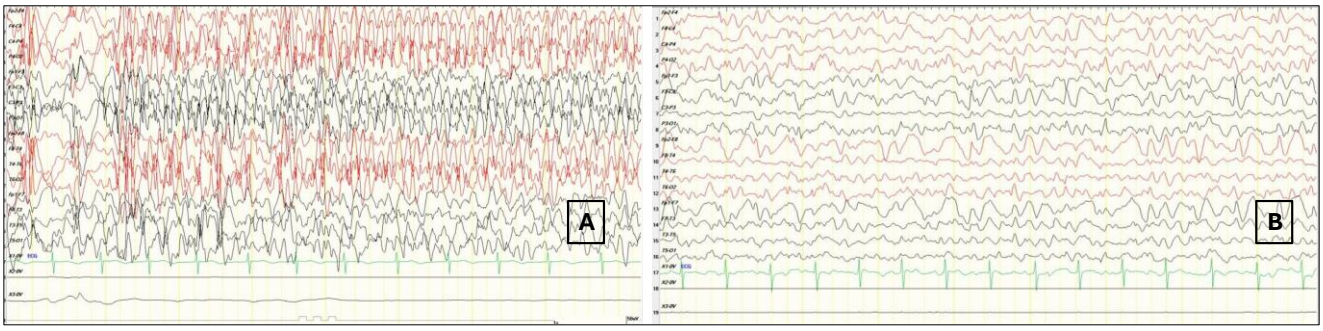

Figure 2: Case 2 (A) EEG of patient with GRIN2D mutation showing generalized spike and polyspike-wave discharges with inappropriate background maturation of age, and (B) following treatment with Memantine and Perampanel, the background appears better organized for age with multifocal epileptiform discharges. Child showed considerable developmental gain following treatment.

Table 1: Summary of cases.

Cases	Gene mutation	Pattern of inheritance	Primary seizure/clinical features	Precision therapy used	Outcome
1	STX1B	De novo , autosomal dominant (heterozygous)	Polymorphic seizures (GTCS, myoclonic, atonic); normal MRI; diffuse encephalopathy	Levetiracetam (10 mg/kg/day)	Seizure control achieved; milestones and academics excelled

Continued.

Cases	Gene mutation	Pattern of inheritance	Primary seizure/clinical features	Precision therapy used	Outcome
2	GRIN2D	Autosomal dominant (heterozygous)	Refractory tonic seizures (onset 2 years); developmental regression; flat background EEG	Perampanel 4 mg/day and Memantine	Marked seizure control and developmental gains; EEG remains abnormal
3	FRRS1L	Autosomal recessive (homozygous)	Focal non-convulsive status epilepticus; macrocephaly; progressive neuro-regression	Perampanel 8 mg/day	Initial 6-month seizure freedom; decline following drug cessation. Reintroduction controlled seizures but development remains stalled
4	KCNC1	Autosomal dominant (maternal carrier)	Neonatal focal clonic seizures; epileptic spasms; choreiform movements; hypsarrhythmia	Fluoxetine (0.5 mg/kg/day)	Reduced spasms; improved alertness, motor control, and vocalization

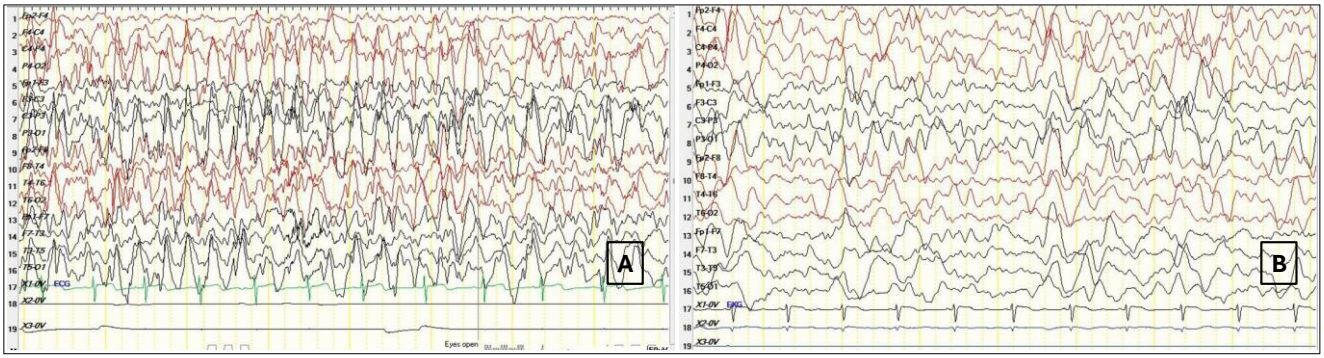

Figure 3: Case 3 (A) EEG of patient with FRRS1L mutation showing continuous runs of high amplitude bioccipital onset epileptiform discharges suggestive of nonconvulsive status epilepticus, and (B) following treatment with Perampanel, there is resolution of NCSE with occasional frontal sharp and slow wave discharges.

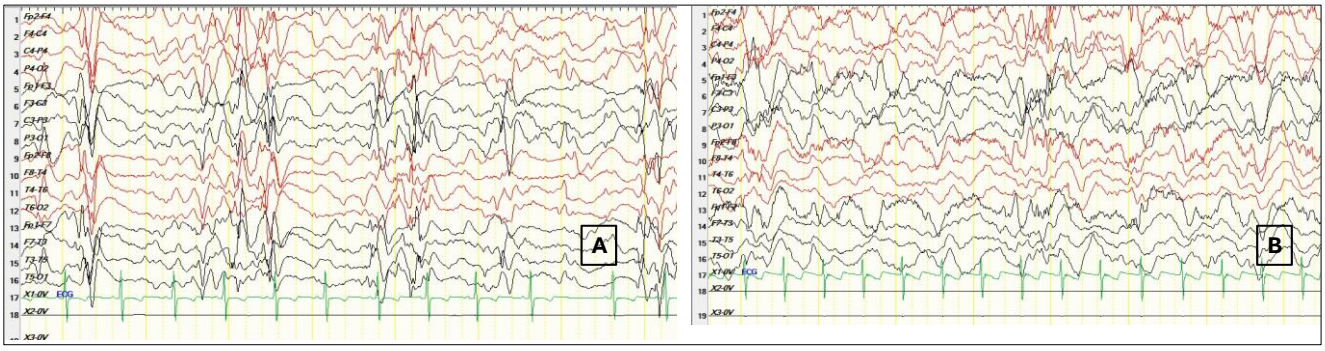

Figure 4: Case 4 (A) EEG of patient with KCNC1 gene showing continuous bursts of high amplitude spike and wave activity with electrodecremental response and lack of sleep spindles suggestive of epileptic encephalopathy with hypsarrhythmia, this was persisting despite hormal treatment with ACTH and steroids, and (B) EEG after treatment with Fluoxetine showing resolution of epileptiform bursts although the background remains abnormal.

DISCUSSION

The most studied ion channel mutation that has accelerated the drive towards precision therapy in epilepsy is perhaps the sodium channel related developmental epileptic encephalopathies, particularly Dravet syndrome. We are well aware that the choice of drug depends on the type of mutation (loss of function versus gain of function) in these channelopathies.[4]

Similarly, there are several other ion channels that have been implicated in the causation of infantile epilepsies where re-purposed medications play a crucial role as exemplified in some of our cases.

STXBP1 encodes syntaxin-1B, a presynaptic SNARE protein essential for neurotransmitter release. Loss of function in STXBP1 gene results in a wide spectrum of

neurodevelopmental maladies ranging from epilepsy only to severe developmental epileptic encephalopathy.[5]

Levetiracetam acts via a novel mechanism on the synaptic vesicle 2A (SV2A) receptor and helps to stabilise the synaptic vesicle, indirectly enhance GABA synthesis and reduce glutaminergic hyperexcitability. Studies on efficacy of Levetiracetam in STXBP1 showed marked reduction in seizure frequency and potentially remission from seizures in early onset cases.[6,7]

With reference to case 2, The N-methyl D aspartate (NMDA) receptors are encoded by the GRIN family of genes. The mechanism by which pathology in the GRIN2D gene causes epileptic encephalopathy is complex.[8] It has been noted that gain-of-function mutations in GRIN2D result in excessive NMDA receptor activity, leading to epileptic encephalopathy with developmental delay.[9]

Memantine is an FDA approved drug for Alzheimer's disease that acts by inhibiting NMDAR over activity mediated by the V667I receptors.[10] There are case reports that show good seizure control with Memantine in children with gain of function GRIN related epilepsies.[11] Perampenel was recently reported in a case report by Li et al as a promising adjunctive therapy in refractory seizures in GRIN2D mutation.[12]

The most interesting and unreported precision therapy is demonstrated in our case number 4. FRRS1L mutations have been reported to cause progressive neuro-regression with epileptic encephalopathy, choreoathetosis and cognitive deficits. The mutation affects glutaminergic signalling by modifying AMPA receptor biogenesis.[13] Existing scientific literature for FRRS1L is limited to case series/reports. Unlike other reported cases, our case did not demonstrate abnormal movements at any stage of the clinical presentation.

Ambrosino et al shared a similar experience of an 8-year-old girl with DRE harbouring a de novo gain of function mutation in KCNC1 gene. She had a dramatic response to low dose oral Fluoxetine at 6 mg/day.[14]

Gain of function mutations cause hyperpolarisation of voltage dependent potassium channels with absence of inactivation. Fluoxetine, an SSRI, commonly used in depression has been noted to show targeted inhibition of open KV3.1 channels.[15]

The role of Fluoxetine has been reported in KCNT1 and KCNC2 related epilepsies as well showing that the drug may be considered for the wider spectrum of potassium gated channelopathies.[16,17]

CONCLUSION

In our series, four patients with different gene defects demonstrated inadequate seizure control with multiple antiseizure medications. Studying the molecular mechanisms of the gene variants and exploring the effect of a given gene defect on neurotransmitter/ion channel functions offers an opportunity for targeted interventions resulting in superior seizure control and often developmental gains. Some of these drugs may not the standard antiseizure medications (as highlighted by the use of Fluoxetine for KCNC1 mutation) opening avenues to try repurposed drugs based on the mechanism of action.

With rapid explosion of genes being discovered, there is a lag in testing potentially helpful drugs. Also, these defects are rare and hence we may not have enough numbers to perform trials for every gene defect. Thus, case reports form an important base to build evidence in this direction. Though our cases are anecdotal, it is helpful to share the strategies (drugs/diet which are successful for a given gene defect) with the paediatric neurology fraternity so that these can be tested by others facing similar predicament. This will help to build further evidence for precision medicine.

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