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Indian Academy of Neurology

Advances in Epilepsy

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CHAPTER 11

Management of Genetic Epilepsies

Jyotsna AS, Bhargavi Sanji, KP Vinayan

ABSTRACT

With the advances in molecular genetics, understanding of genetic epilepsies and their underlying mechanisms have evolved tremendously, making a significant impact on the therapeutic decision-making. Subsequently, epilepsy management in children is slowly evolving from an epilepsy syndrome-based generic approach to an individually targeted approach, based on the underlying etiopathophysiologic mechanism. In this chapter, we present an overview of the current status of this ongoing paradigm shift in genetic epilepsies with a focus on those epilepsies that have an option of specific targeted treatments, which is of great relevance for neurological practice.

Keywords: Genetic epilepsies, Precision medicine, Epilepsy genes.

INTRODUCTION

Genetic epilepsies are estimated to constitute approximately one-third of all epilepsies.[1] The 2017 International League Against Epilepsy (ILAE) classification of epilepsies conceptually defines genetic epilepsy as an epilepsy that results directly from a known or presumed genetic mutation in which seizures are a core symptom of the disorder.[2] Pragmatically, a genetic etiology for epilepsy may be inferred in the situation of a strong family history (especially autosomal dominant inheritance) or by clinical research in populations with the same syndrome/familial aggregation studies or when a genetic variant (single gene mutation/copy number/chromosomal aberration) is reproducibly associated with an epilepsy phenotype. Genetic epilepsies include epilepsies with monogenic (de novo or inherited pathogenic variants) or complex (polygenic with or without environmental factors) inheritance.[3]

The latest ILAE classification system proposed in 2022 describes epilepsy syndromes based on the age of onset, and genetic etiologies are enumerated under each epilepsy syndrome phenotype (e.g., infantile epileptic spasms syndrome and developmental/epileptic encephalopathy, etc.). Certain gene-specific epilepsy syndromes are also defined due to pathogenic variants in a single gene [e.g., *CDKL5* developmental and epileptic encephalopathy (CDKL5-DEE), *PCDH19* clustering epilepsy, glucose transporter 1 (GLUT1) deficiency syndrome—DEE and KCNQ2-DEE, etc.]. This chapter provides a brief overview of the current status of precision medicine in the epilepsies and suggests the adoption of a pragmatic approach.

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Genetic generalized epilepsies are associated with a complex polygenic pattern as well as a significant environmental contribution. Moreover, structural focal epilepsies like focal cortical dysplasia (FCD) might also be associated with somatic mutations in the affected tissues. A detailed discussion on the management of both these syndromes with genetic underpinnings is beyond the scope of this chapter. Monogenic multiaxial neurological disorders (e.g., progressive myoclonus epilepsies) and multisystem diseases (e.g., lysosomal storage disorders) also may be viewed as a category of genetic epilepsy, though epilepsy may constitute only a part of the disease phenotype. Some of the diseases in this group are now amenable to targeted therapies. From the utilitarian perspective, this chapter will mention these disorders only if there is some role for precision medicine currently.

CLASSIFICATION OF GENETIC EPILEPSIES

Classification of genetic epilepsies may be approached in multiple ways. Pragmatically, a listing out of genes associated with various syndromes serves as a ready reckoner for a practicing neurologist. The major epilepsy syndromes and genes associated with them are enlisted in **Figure 1**. However,

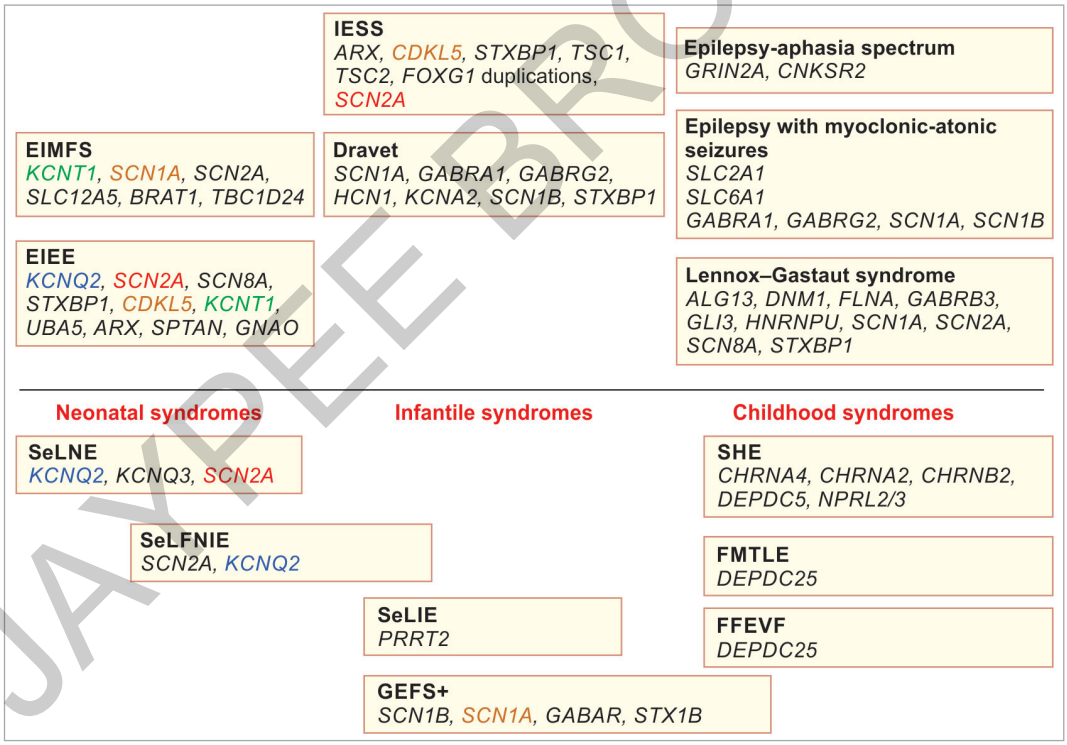

FIG. 1: Classification of genetic epilesies based on the electroclinical phenotype.

(EIEE: early infantile epileptic encephalopathy; EIMFS: epilepsy of infancy with migrating focal seizures; FFEVF: familial focal epilepsy with variable foci; FMTLE: familial mesial temporal lobe epilepsy; GEFS: genetic epilepsy with febrile seizures; IESS: infantile epileptic spasms syndrome; SHE: Sleep-related hypermotor epilepsy; SeLFNIE: self-limited familial neonatal-infantile epilepsy; SeLIE: self-limited infantile epilepsy; SeLNE: self-limited neonatal epilepsy)

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TABLE 1: Classification of genetic epilepsies based on the etiopathology.

Pathomechanism	Examples
Ion channel or receptor defects	Sodium and potassium channel mutation-related epilepsies
Signaling pathway defects	m-TORopathies (tuberous sclerosis epilepsy)
Metabolic pathway defects	
Inborn errors of metabolism with epilepsy as a dominant/only phenotype	Pyridoxine-dependent epilepsy
Multiaxial neurological syndromes with epilepsy	Progressive myoclonus epilepsies and chromosomal disorders (ring chromosome 20-related epilepsy)
Multisystem disorders with epilepsy	Lysosomal storage diseases

(m-TOR: mammalian target of rapamycin)

from the perspective of understanding and management of genetic epilepsies, a classification by the pathomechanisms involved is more meaningful. **Table 1** gives an overview of the epilepsies based on the pathomechanisms involved, with suitable examples.

PRECISION MEDICINE IN GENETIC EPILEPSIES

"Precision medicine is an innovative approach that uses individual's genomic, environmental, and lifestyle information to guide decisions related to their medical management." With increasing knowledge on etiopathomechanisms of genetic epilepsies, precision medicine has taken center stage in the management of many well-defined genetic epilepsy syndromes. Precision medicine can be classified into various levels based on the therapeutic target. While most monogenic epilepsies may not be currently amenable to precision therapy, a proper diagnosis can still provide valuable phenotypic and prognostic information and can guide toward further evaluation and management (e.g., cardiac evaluation in *SCN1A*-associated Dravet syndrome and the use of sleep electroencephalography for detecting electrical status in sleep in *KCNB1*-related epileptic encephalopathy). **Figure 2** shows the tiers/levels in precision medicine, with examples of genetic epilepsies. In **Table 2**, the genetic epilepsies amenable to precision treatment are enumerated.

CHALLENGES IN MANAGEMENT OF GENETIC EPILEPSIES

Several challenges at multiple levels may be encountered in the management of genetic epilepsies. Phenotypic and genotypic heterogeneity is one such challenge. Phenotypic heterogeneity is where several types of mutations can occur in a single gene manifesting into multiple epilepsy phenotypes, and this can be exemplified by the *SCN1A* gene-related epilepsy spectrum which may result in febrile seizures, Dravet syndrome, and genetic epilepsy with febrile seizures (GEFS) plus phenotype.[4] Increased access to the next generation sequencing has resulted in the discovery of several such genes with a varied spectrum of epilepsy and neurological disorders.[5] Genotypic heterogeneity is when one epilepsy phenotype is associated with a number of different genes, which is best exemplified by the infantile epileptic spasms syndrome (IESS) that may be associated with multiple gene

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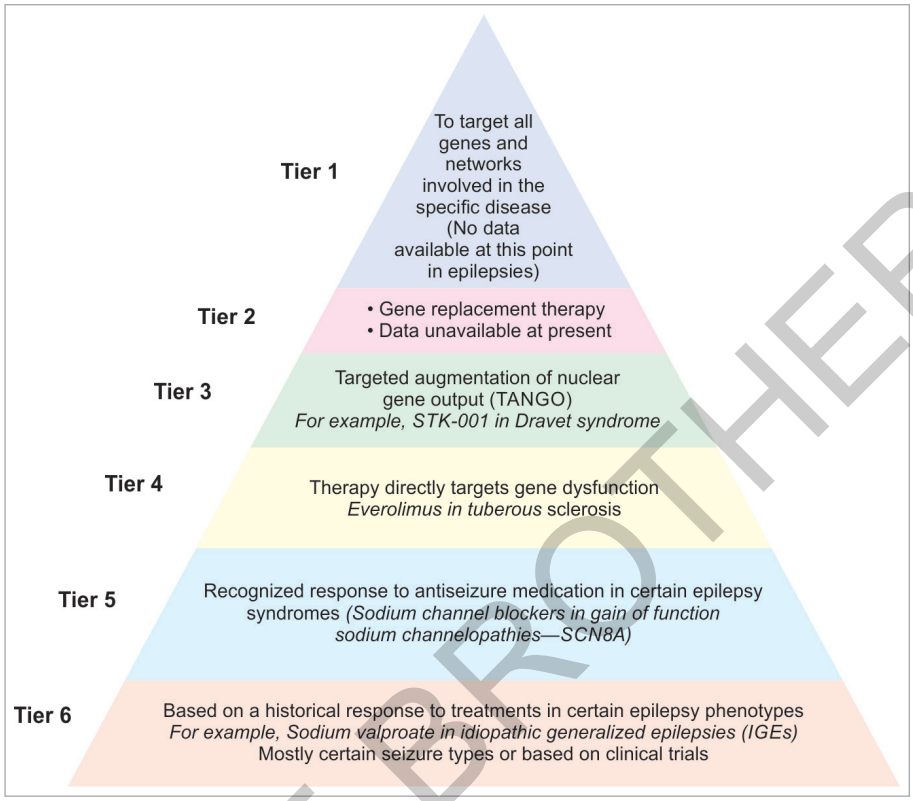

FIG. 2: Tiers/levels in precision medicine, with examples of genetic epilepsies.

TABLE 2: Genetic epilepsies amenable to precision treatment.

	Gene	Epilepsy syndrome	Treatment
Ion channels and receptors and others			
Sodium channel	*SCN2A*	• *Early onset:* BFNIE, DEE, and EIMFS—GoF • *Late onset:* Autism with seizures—LoF	• SCB: Phenytoin and CBZ • SCB may worsen
	SCN8A	• *Early onset:* Severe/moderate DEE and SeLFIE— GoF • *Late onset:* NDD with generalized epilepsy—LoF	• SCB: CBZ and OxCBZ • *SCB*: May worsen • *DOC:* Valproate, lamotrigine, and ethosuximide
	SCN1A	Dravet syndrome	• Valproate, clobazam, stiripentol, fenfluramine, and cannabidiols • Avoid SCB
Potassium channel	*KCNQ2*	BFNIE and DEE/EE	SCB and retigabine
	KCNT1	ADNFLE and EIMFS	Quinidine

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	Gene	Epilepsy syndrome	Treatment
NMDA receptor	*GRIN2A*	SeLECTS, LKS, and CSWS	Memantine
	GRIN2B	West syndrome and LGS	Memantine
Others	*PRRT2*	SeLIE and PKD	SCB
	CDKL5	EIEE and IESS	Ganaxolone
	KATP	Developmental delay, epilepsy, and neonatal diabetes	Sulfonylurea
Inherited metabolic disorders			
Pyridoxine metabolism pathway	*ALDH7A1*	Neonatal onset drug-resistant seizures	• Pyridoxine ± folinic acid • Arginine, Lysine restricted diet
	PNPO		PLP ± Pyridoxine
Biotinidase deficiency	*BTD*	EIEE/DEE	Biotin
Glucose transporter deficiency	*GLUT1*	• Early onset absences • Myoclonic absences	Ketogenic diet
Cerebral folate deficiency	*FOLR1*	Developmental delay/regression ± epilepsy	Folinic acid
Creatine deficiency syndrome	*GAMT* *SLC6A8* *AGAT*	Autism with epilepsy	Creatine, arginine-restricted diet, and ornithine
Serine biosynthesis disorders	*3-PGDH* *PSAT* *PSP*	Microcephaly and drug-resistant epilepsy	• Serine • Glycine
Folate metabolism	*DHFR* *FR*	Developmental delay and hypotonia	Folinic acid
Menkes disease	*ATP7A*	Progressive neurodegeneration	Copper histidine
CoQ10 (ubiquinone) deficiency syndromes	*C0Q2,4* *PDSS1*	Multisystem involvement	CoQ10
mTOR signaling pathways			
Tuberous sclerosis	*TSC1/TSC2*	Varied presentations	*mTOR inhibitors:* Everolimus
GATORopathies	*DEPDC5* *NPRL2* *NPRL3*	Lesional and nonlesional epilepsy	*mTOR inhibitors:* Everolimus

(ADNFLE: autosomal dominant nocturnal frontal lobe epilepsy; BFNIE: benign familial neonatal-infantile epilepsy; CBZ: carbamazepine; CSWS: continuous spikes and waves during sleep; DEE: developmental and epileptic encephalopathy; DOC: drug of choice; EIEE: early infantile epileptic encephalopathy; EIMFS: epilepsy of infancy with migrating focal seizures; EE: epileptic encephalopathy; GoF: gain-of-function; IESS: infantile epileptic spasms syndrome; LKS: Landau–Kleffner syndrome; LGS: Lennox–Gastaut syndrome; LoF: loss-of-function; NDD: neurodevelopmental disorders; NMDA: N-methyl-D-aspartate; PKD: paroxysmal kinesigenic dyskinesia; SCB: sodium channel blockers; SeLECTS: self-limited epilepsy with centrotemporal spikes; SeLFIE: self-limited infantile epilepsy)

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mutations like *KCNB1*, *KIF1A*, *SLC35A2*, *STXBP1*, *TBL1XR1*, and others.[6] **Figure 1** elucidates different epilepsy syndromes along with the associated genes. As a result, a specific mutation may not equate immediately to the diagnosis of a specific epilepsy syndrome. Furthermore, different pathogenic variants of the same gene can result in opposite functional effects, which has a bearing on the efficacy of therapy with certain classes of medication. A good example is *SCN2A*-related epilepsies where gain-of-function (GoF) mutations can be successfully treated with sodium channel blockers. On the contrary, sodium channel blockers may aggravate seizures related to loss-of-function (LoF) variants of the same *SCN2A* gene. Different mutations are known to cause different effects on the translated protein or downstream pathway, which may result in either a gain or loss of the protein's function.[7] Uncertainty in the pathogenicity of a mutation may lead to difficulties in decision-making and the answer to this problem may lie in the discovery of doable functional studies, which are still to evolve yet. A better understanding of the epileptic syndromes, the epilepsy genes, and the functional implications of their pathogenic variants are critical for the selection of antiseizure medication and also for development of novel therapies. In keeping with the explosion of information regarding the disease-causing genes, a periodic reevaluation of reported variants also is necessary at regular time intervals to deliver optimal patient care.

Cases 1 to 3 show illustrative examples of different types of genetic epilepsies and the vagaries in their presentation, natural history, and practical issues associated with decision-making.[8]

CASES

CASE 1

A 3-month-old baby with an uneventful perinatal period and normal development was brought with history of seizures from 10th day of life. The seizures as observed by the parents was of varied semiology. Predominantly, focal tonic and multifocal clonic type of seizures were described. EEG showed a normal background activity and sleep patterns. MRI was normal. The child had been initiated on levetiracetam and referred to a pediatric epilepsy center in the 3rd month of life in view of an abrupt increase in the seizure frequency to multiple daily brief seizures in a single week. Family history revealed similar seizures during infancy in the father and paternal uncle, which had abated by 2nd year of life. Oxcarbazepine was initiated, following which there was a complete cessation of seizures. Parents were anxious that the child may have recurrence of seizures and would watch the child through the night. NGS for epilepsy gene panel was sent, which showed a pathogenic variant in *SCN2A* gene. Parental segregation revealed the same variation in the father. Parents were counseled about the probability of self-limited nature of the child's epilepsy. It allayed the fear of withdrawal of antiseizure medication. Levetiracetam was withdrawn in 5th month of life. Oxcarbazepine was tapered off at 18 months of age. The child is presently developmentally normal and performing well at school.

(EEG: electroencephalogram; MRI: magnetic resonance imaging; NGS: Next-generation sequencing)

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CASE 2

A 4-month-old baby girl, born to consanguineous parents, with uneventful perinatal period was brought with complaints of paroxysmal events from 2 weeks of life. Mother described shock-like jerks in clusters, especially on awakening. She had apparently lost social smile and her usual playfulness after the onset of the events. There was a family history of sibling death following severe developmental delay and epilepsy. On examination, child was noted to have poor visual fixation with a mild hypotonia. Patchy scalp alopecia noted. There were no other skin manifestations. The routine metabolic parameters were normal. Prolonged VEEG captured several habitual electroclinical events suggestive of epileptic spasms, and the interictal record was suggestive of modified hypsarrhythmia. MRI brain was normal. The child was initiated on ACTH therapy, and after a week, a 50% reduction in the spasm frequency was reported. Pyridoxine and valproate were initiated. Whole exome sequencing was done in view of it being a cryptogenic West syndrome, and it showed a likely pathogenic homozygous variant in *BTD* gene. She was initiated on biotin, and within a week, there was complete cessation of spasms. The child's developmental milestones also improved, but at the age of 3 years, she is yet to speak sentences, and walks with a mild unsteadiness of gait.

(ACTH: adrenocorticotropic hormone; MRI: magnetic resonance imaging; VEEG: video electroencephalogram)

CASE 3

A 3-year-old boy was referred to a pediatric epilepsy unit with history of absence seizures since 6 months, which persisted despite 3 antiseizure medications. He was born to nonconsanguineous parents with an uneventful perinatal period. The child was reported to have mild developmental delay when compared to the older sibling. There was no family history of seizures. Detailed probing into the seizure history revealed that the child had a few seizures in the past, which were suggestive of myoclonic and brief focal seizures, and these events had been noted specially in morning times. Parents also reported some unusual eye movements during infancy. Homemade videos of such events were noted to show rapid multidirectional eye movements accompanied by head movements in the same direction. The child's head size was less than third centile for age, while neurological examination was otherwise unremarkable. Video EEG captured multiple electroclinical events suggestive of atypical absence seizures. MRI brain was normal. Glucose transporter 1 (GLUT1) deficiency syndrome was suspected. CSF study revealed significant hypoglycorrhachia. Clinical exome sequencing showed a pathogenic mutation in *SLC2A1*, confirming the diagnosis of GLUT1 deficiency syndrome. Ketogenic diet was initiated which led to remarkable reduction in the seizure burden. However, the child's cognitive status continued to be subnormal for age, and during follow-up he was reported to be significantly below par in academic performance at school.

(CSF: cerebrospinal fluid; EEG: electroencephalogram; MRI: magnetic resonance imaging)

CONCLUSION

Marked expansion in the number of epilepsy-related genes has drastically impacted the outlook toward epilepsy therapeutics. This is well illustrated by precision medicine triumphs in some classically described genetic epilepsies (e.g., *ALDH7A1*-associated pyridoxine-dependent epilepsy and *SLC2A1*-associated GLUT1 deficiency syndrome). However, a successful treatment paradigm after genetic confirmation is not yet available for majority of genetic epilepsies. Better understanding of gene mutation–treatment response relationships will definitely help facilitate better selection of antiseizure medications.

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