Original Article

Genome-Based Therapeutics: Era of Precision Medicine in Genetic Epilepsies and Epileptic Encephalopathies

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Abstract

Introduction: The recent evolution of genomics has led to the development of targeted therapeutics, revolutionizing medical approaches. This study aimed to assess the impact of genetic testing on the current epilepsy management paradigm with a specific focus on the variability of outcomes subsequent to genetic diagnoses. **Methodology:** Data were collected retrospectively from a cohort of children aged 1–18 years, diagnosed with refractory epilepsy of confirmed genetic origin. The participants received care at a quaternary care center's pediatric neurology clinic from August 2019 to June 2021. The collected information included demographic characteristics, seizure types, EEG findings, imaging abnormalities, genetic diagnoses, attempted treatments, and seizure outcomes. **Results:** Among the 210 children with confirmed genetic diagnoses, 74 were included in the study. The gender distribution comprised 45 males and 29 females. Within the cohort, 68/74 exhibited single gene variations, with 23 cases associated with sodium/potassium/calcium channelopathies. Precision medicine could be applied to 25/74 cases. 17/74 children (22.97%) experienced a reduction of up to 50% in seizure frequency due to precision medicine implementation. **Conclusion:** While our study indicates the significance of genetic insights in adapting treatment approaches for pediatric epilepsy, it is important to temper our conclusions. The retrospective nature of our study confines our ability to definitively gauge the extent of precision medicine's utility. Our findings suggest the potential of genetic information to enhance epilepsy management, but the true impact of precision medicine can only be established through prospective investigations.

Keywords: Developmental and epileptic encephalopathies, genetic epilepsies, precision medicine

Introduction

The present generation heavily relies on the genetic basis for understanding our behavior, health, and the causes of diseases. For intractable epilepsies, there is newfound hope for treatment. Precision medicine appears to be the future formula for treating epilepsy, offering tailored medical approaches and minimizing unnecessary investigations. However, we must also remain cautious about the potential for exploitation. While not all genetic epilepsies directly influence the choice of drugs, decoding the genes involved is undoubtedly a revolutionary step toward successful management and achieving seizure freedom.

Several conditions like Dravet syndrome, pyridoxine-dependent epilepsy, and glucose transporter 1 deficiency now have definitive treatments for controlling seizures after being genetically diagnosed.[1]

Our objective was to assess the impact of genetic testing on the current approach to epilepsy, with a focus on understanding the variability of outcomes following genetic diagnoses. We conducted a retrospective cohort study at a single center involving children with diagnosed genetic epilepsy.

Methodology

This retrospective cohort study spanned a duration of 2 years from August 2019 to June 2021 and involved 74 children diagnosed with confirmed genetic epilepsies/epileptic encephalopathies. The study was conducted at the Department of Pediatric Neurology and Genetics within a quaternary care center. Over the study period a total of 3,840 children presented with epilepsies of various etiologies including structural, metabolic, and inflammatory causes. Among them, 768 children were clinically suspected to have a probable genetic etiology due to factors such as positive family history, normal MRI results, and the absence of other identifiable causes. 210/768 children agreed to undergo genetic testing. Of the 210, 156 children had refractory epilepsy while 54 had developmental delays along with epilepsy. From this pool, we selected 74 children with pathogenic and likely pathogenic variants based on the American College of Medical Genetics and Genomics criteria. Additionally, 136 children had variants

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of uncertain significance making it challenging to establish causality.

The inclusion criteria encompassed children aged 1 month to 18 years with a confirmed genetic etiology for refractory epilepsy [Figures 1 and 2]. The data collection process included gathering demographic details, age of presentation, seizure semiology, neurological features, epilepsy type, neuro-imaging, and electroencephalographic characteristics as well as the genetic diagnosis. Seizure frequency was defined in accordance with the American Academy of Neurology quality measures: innumerable (i.e., >10/day for most days), multiple per day (i.e., >2 seizures/day for 4 days a week), daily (i.e., 4 or more days/week), weekly but not daily (i.e., 1–3 per week), and monthly but not weekly (i.e., 1–3 per month). Data regarding the number of children experiencing up to a 50% reduction in seizure frequency following the initiation of precision therapy were also recorded. These children were followed up for a minimum of 3 months and a maximum of 2 years.

Results

Out of 210 children with genetically confirmed epilepsies/epileptic encephalopathies, 74 were included. The gender distribution was 45 males and 29 females. Among the cohort, 15/74 (20%) had a family history of seizures, and 20/74 (27%) were born of 3rd or 4th degree consanguineous marriages. Additionally, 25/74 (33.7%) exhibited dysmorphism and 12/74 (16.2%) had microcephaly. Neuroimaging abnormalities were present in 22/74 (29.72%) cases, including conditions such as lissencephaly, parieto-occipital atrophy, and cortical tubers in cases of tuberous sclerosis depicted in [Table 1].

32/74 (43.24%) children had epileptic encephalopathy, 27/74 (36.5%) had focal epilepsy and 15/74 (20.2%) had generalized epilepsy. Among the 74 children, 59 had global developmental delay, 7 exhibited isolated cognitive delay, 4 had motor delay, and 4 displayed normal development. The mean follow-up period was nine months, and the average number of anti-seizure medications used was 3.

The most frequently encountered scenario involved single gene variants in 68/74 (92%) cases, with 23/74 (33.8%) patients having channelopathies linked to sodium/potassium/calcium channel gene mutations. Neurocutaneous syndromes were identified in 9.45% of children in the study, with conditions like tuberous sclerosis and incontinentia pigmenti exhibiting mutations in TSC1 and IKBKG genes, respectively. Additionally, 8% of epilepsy cases had a chromosomal basis contributing to developmental delay and seizures.

The Table 2a-c enlists the cases presented with developmental delay and epileptic encephalopathy (DEE). Children with genes like TUBB4, TBCD, PEX10, etc. mimicked DEE in their earlier stages.

SCN2A and SCN8A mutations were associated with cluster polymorphic seizures that were refractory but responded to sodium channel blockers. ATP1A2 and ATP1A3 mutations were linked to focal seizures with hemiparesis, while EEF1A2 mutations manifested as myoclonic seizures and absences. IKBKG mutations were tied to generalized cluster seizure episodes. PCDH19, GABRA1, and CACNA1A mutations were connected to prolonged febrile seizures, wherein sodium channelopathy was suspected. Chromosomal mutations were linked to global delay and polymorphic seizures.

Among the 74 children with a genetically identified cause for epilepsy, precision medicine was implemented in 33.7% of cases (25 children) for optimizing anti-seizure medications. The results are depicted in the table below [Table 3].

Up to a 50% reduction in seizure severity was achieved in 17 cases (1-PNPO, 3-SCN1A, 3-SCN2A, 2-SCN8A, 2-KCNQ2, 2-ATP1A2/1A3, 4-tuberous sclerosis). One child with SCN1A required vagal nerve stimulation for seizure control. Among children with tuberous sclerosis, 1 out of 8 underwent tuber resection, achieving seizure freedom for the past 15 months, and 6 out of 8 received everolimus.

Discussion

With the emergence of diagnostic genetics, there is a renewed interest in exploring precise management for challenging-to-treat epilepsies. However, it is crucial to adopt a systematic and pragmatic approach to genetic

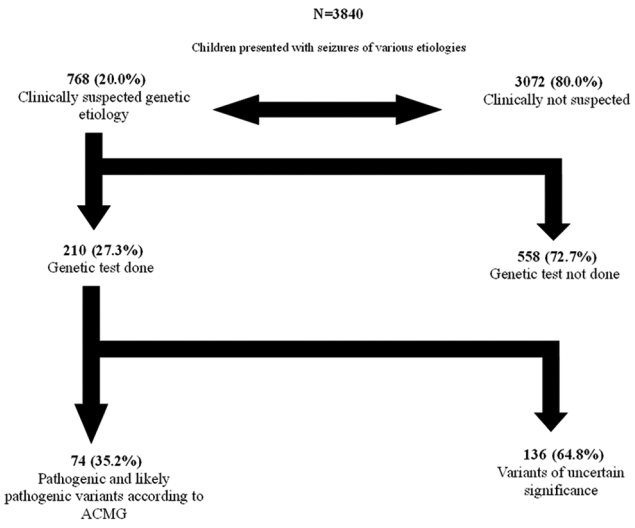

Figure 1: Showing the study population

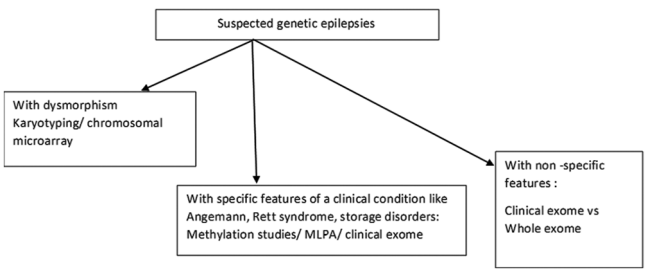

Figure 2: Methods of genetic testing used in the study population

Table 1: Neuroimaging abnormalities

Neuroimaging Abnormalities	Number of Cases (%)
Normal MRI	52 (70.2)
Structural Specific Abnormalities	16 (21.62)
Cortical tubers	7 (9.4)
Multicystic encephalomalacia (Molybdenum Co-factor deficiency)	2 (2.7)
Lissencephaly	1 (1.35)
Thalamic hypodensity and Periventricular hyperintensity	2 (2.7)
Unidentified bright objects (UBO)	2 (2.7)
Hypomyelination with atrophy of basal ganglia and cerebellum	2 (2.7)
Structural Non-Specific Abnormalities	6 (8.1)
Corpus callosum thinning, diffuse cerebral atrophy	

Table 2a: Genetic etiologies that were identified

Gene	Number (% of cases)
Single gene disorders	68 (92%)
A. Channelopathies (sodium/potassium/calcium)	23
B. Neurocutaneous	9
C. Storage disorder	3
D. Other single gene disorders	33
Chromosomal abnormalities included trisomy 21 (3), 8p deletion (1), 9p duplication (1), 1p36 deletion (1)	6 (8%)

Table 2b: List of Genetic Mutations Identified and classified according to American college of medical genetics and genomics (ACMG)

Pathogenic (Class I)	Likely pathogenic (Class II)
PNPO (2 cases)	EEF1A2 (1 cases)
PCDH19 (2 Cases)	PEX10 (1 cases)
TPP-1 (2 cases)	PRRT2 (2 Cases)
ARX (2 cases)	FRRS1L (2 cases)
IKBKG (1 cases)	TBCD (2 cases)
TSC-2 (8 cases)	TUBB4 (1 cases)
SCN1A (8 cases)	CACNA1A (3 cases)
SCN2A (4 cases)	
SCN8A (2 cases)	
KCNT1 (2 cases)	
KCNQ2 (4 cases)	
Mo co-factor (2 cases)	
ATP1A2 (2 cases)	
ATP1A3 (3 cases)	
MECP2 (3 cases)	
ARV1 (2 cases)	
CDLK5 (2 cases)	
STXBP1 (2 cases)	
GABRA1 (3 cases)	

diagnosis. The fundamental concept of precision medicine entails personalizing treatment to target the precise molecular pathogenesis of a given condition. The present study highlights two pivotal aspects concerning refractory epilepsy in the pediatric age group: the notable prevalence of genetic abnormalities within the DEE spectrum and the judicious harnessing of this genetic information to achieve effective seizure control through precision medicine. Conditions that initially mimic DEE often include storage disorders as well as hypomyelination with atrophy of basal ganglia and cerebellum.

Previous studies on early childhood onset genetic epilepsies indicated a yield of 80 out of 333 (34.3%).[1] Another study focusing on infantile-onset epileptic encephalopathies from India revealed a yield of 26 out of 82 (31.7%).[2] Upon the identification of specific genetic abnormalities, the underlying mechanisms were broadly categorized into ion channels, vesicular trafficking and transmission, transporter function, enzymatic function, and gene function modification.

The ion channels pinpointed in our study encompassed SCN-related mutations, encompassing both gain and loss of sodium channel function (from SCN1A-related Dravet syndrome to SCN2A and SCN8A). SCN1A-related epilepsy manifests a wide spectrum from Generalized Epilepsy with Febrile Seizures Plus (GEFS+) at the milder end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures (IGE-GTC) at the severe end.[3,4] In cases with loss of function mutations, sodium channel blockers were avoided. In the present study, vagal nerve stimulation (VNS) partially controlled seizures in only one child. Becampanel and Glycosamide showed the best response in focal seizures, as observed in previous reports, while Carbamazepine and Phenytoin (sodium channel blockers) worsened seizures.[4] In a study by Fulton *et al*., VNS achieved >50% reduction in seizures in 4 out of 12 children with generalized tonic-clonic seizures.[5] Cannabidiol, though not specific to Dravet syndrome, was used with limited experience. Stiripentol and Fenfluramine are proposed treatments, but availability and compliance pose limitations. Ongoing human trials involve STK001 (an antisense oligonucleotide that increases SCN1A mRNA), EPX-100 (Clemisole - an antihistamine), and EPX-200 (Lorcaserin - Serotonin signaling pathway).[6]

SCN8A is associated with a broad clinical spectrum, including early onset severe DEE (Developmental epilepsy and epileptic encephalopathies). Patients with SCN8A-related epilepsy achieved seizure freedom with phenytoin and carbamazepine. GS967, a novel sodium channel blocker, is currently in animal trials.[7]

KCNQ2-related epilepsies formed another group of ion channel disorders identified in our population. Among 8 children with KCNQ2-related epilepsy, 3 achieved control with lacosamide and sodium valproate, though they exhibited cognitive delay with autistic traits. Early onset epileptic encephalopathy variants showed a positive response to a ketogenic diet (reducing daily tonic seizures from 10/day to 2/day). KCNQ2-related epilepsy is classified into benign variants that respond to Phenobarbital and sodium channel blockers for benign and EOEE variants.[8,9]

Table 2c: Epilepsy syndromes and the mutations identified in our cohort

Epilepsy syndromes	Mutations identified ($n=74$)
Early infantile and developmental epileptic encephalopathy	PNPO, KCNQ2, PEX10, PRRT2
Infantile epileptic spasm syndrome	PNPO, Mo co-factor, TSC2, ARX, STXBP1, trisomy 21
Lennox gastaut syndrome	KCNT1, KCNQ2, ARV1, CDLK5
Dravet and Dravet like presentation	SCN1A, GABRA1, PCDH19, CACNA1A
Epilepsy in infancy with migrating focal seizures	KCNT1
Developmental epileptic encephalopathy with spike-wave activation in sleep	CACNA1A, MECP2, FRRS1L, TBCD, TUBB4
Progressive myoclonus epilepsy	TPP1

Table 3: Mutations and Precision Medicine Applied

Genetic mutation identified	Number of cases $n=25$	Precision medicine applied
PNPO	2	Pyridoxal phosphate supplementation
SCN1A	8	Avoidance of sodium channel blocker, Ketogenic diet
SCN2A	4	Adding sodium channel blocker
SCN8A	2	Carbamazepine, High dose of phenytoin
KCNQ2	4	Na channel blockers 2 out of 8- Ketogenic diet
ATP1A2/1A3	5	Topiramate

Two girls with PCDH19 mutations were identified. Although precision medicine's complete understanding for this mutation is lacking, the use of Bromide/Clobazam has been mentioned in previous literature. In our study, we observed a positive response with phenobarbitone.[10,11]

PRRT2 mutations belong to the vesicle trafficking, synaptic vesicle formation, and transmission subgroup. While initially described as a cause of benign familial infantile seizures, the entity has broad implications that extend beyond this characterization.[12] In our study two children with PRRT2 related refractory epilepsy were identified. Notably, the genes altering enzymatic function included PNPO, characterized by a homozygous mutation in the highly conserved exon 3: c.352G > A p. Gly118R. An intriguing aspect of this mutation was its unique responsiveness to thiamine, riboflavin, and pyridoxal phosphate.[13]

Regarding gene function modification, the TSC2 gene emerged as a prominent player particularly within the mTOR pathway. Everolimus exhibited antiepileptogenic effects by altering signaling pathways, protein expression, and downstream mechanisms implicated in epileptogenesis. Our study demonstrated the efficacy of Everolimus in reducing seizure frequency among cases of tuberous sclerosis complex, with a positive response in 4 out of 8 cases.[14] Vigabatrin, employed for treating infantile spasms and focal seizures linked to tuberous sclerosis was also utilized for presymptomatic children with ictal/interictal EEG abnormalities, though our experience in this realm remains limited.[15]

A study by Balestrini *et al*. reported a modest 3% positive outcome (seizure reduction >50%) using the precision medicine approach.[16] While our study encompassed a heterogeneous age range from 1 month to 18 years, the commonality of seizure onset during infancy and early childhood drove our exploration of genetic bases and precision medicine concepts. However, it is important to acknowledge that our study's scope does not permit the generalization of results to a larger cohort. Future endeavors should encompass community-based and prospective studies to comprehensively grasp the magnitude of this issue within our country's context.

Conclusion

While our study indicates the significance of genetic insights in adapting treatment approaches for pediatric epilepsy, it is important to temper our conclusions. The retrospective nature of our study confines our ability to definitively gauge the extent of precision medicine's utility. Our findings suggest the potential of genetic information to enhance epilepsy management, but the true impact of precision medicine can only be established through prospective investigations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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