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Epileptic Disorders

ORIGINAL ARTICLE

Clinical and genetic evaluations of rare childhood epilepsies in Turkey's national cohort

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Abstract

Objective: As new-generation sequencing methods develop, rare epilepsy is increasing and burdening national health systems—community building among rare epilepsies fuels collaboration, research, and resource development. Comorbidities should be carefully considered in diagnosing and treating children with rare epilepsy. This multicentric study aimed to evaluate the clinical features and comorbidities of children diagnosed with rare childhood genetic epilepsies.

Methods: This multicentric study evaluated demographics, clinical findings, neuromotor developmental progress, and concomitant comorbid diseases of childhood rare genetic epilepsies. We included 156 patients from the nine tertiary health centers in our research.

Results: The gene variants were distributed to 36 patients (23.1%) with SCN1A, 14 (9%) with KCNQ2, 10 (6.4%) with PCDH19, 6 (3.8%) with SCN8A, 5 (3.2%) with SLC2A1, 5 (3.2%) with WWOX, respectively. The remaining 80 patients (51.3%) were with other gene variants. Comorbid conditions are present in 82% of patients, most commonly intellectual disability (70%), developmental delay (32.1%), and movement disorders 12.8%. Most of the rare genetic epileptic children (52%) were using more than three anti-seizure drugs. In terms of developmental delay

See Appendix 1 for the Turkish Rare Epilepsies Study Group.

in children with rare epilepsy, the neuromotor developmental delay was found to progress with age, shown at the end of 2nd year of treatment. In addition, comorbidity, number of drugs, multiple types of seizures, seizure frequency, age at diagnosis of epilepsy, and duration of epilepsy all affected neuromotor developmental status ($p < .05$).

Significance: Despite using multiple antiseizure medications, most of our patients had drug-resistant epilepsy and concomitant developmental delay. Since a complete cure cannot be achieved in most of these patients further studies with centers' collaboration might help improve therapeutic decisions and precision treatment methods.

KEYWORDS

childhood, comorbidity, genetic, precision medicine, rare epilepsy

1 | INTRODUCTION

As new-generation sequencing methods develop, the incidence of rare epilepsy is increasing. Next Generation Sequencing (NGS) and whole exome sequencing (WES) have led to the identification of more and more genes. Currently, approximately 30%–40% of epilepsy syndromes can have an associated genetic mutation, and this number is increasing. Community building among rare epilepsies fuels collaboration, research, and resource development.[1]

The growth, breadth, and complexity of rare epilepsies underscore the importance of measuring the incidence and prevalence, as well as the national public health burden. The estimated annual incidence of single-gene epilepsies in the well-defined population is 1 in 2120 live births.[2]

The prevalence of multiple comorbidities in children with rare epilepsy, especially those diagnosed with epilepsy in the first year of life, is high and medically complex. Comorbidities should be carefully considered in the diagnosis and treatment of children with rare epilepsy.[3]

In the majority of rare cases, there is no cure. The list of comorbidities in these diseases – many of which have more disabling seizures—continues to expand and an increased risk of premature death. Precision medicine (PM) is a treatment approach in which disease treatment and prevention are tailored to individual variability in genes, environment, and lifestyle for each person. The common feature of the new therapeutic approaches is their attack on PM, which aims to evaluate patients holistically and treat them accordingly.[4] For instance, treatment-oriented scientific investment and research are still required for seizures and comorbidities.

New trends in epilepsy treatment are the development of innovative pharmacological and nonpharmacological approaches given a targeted approach, aiming at improving the symptoms of patients and their quality of life (QoL), together with that of the caregivers.[4] This multicentric study aimed to evaluate the clinical features and comorbidities of children diagnosed with rare childhood genetic epilepsies.

Key points

- In this cohort, SCN1A, KCNQ2, PCDH19, SCN8A, SLC2A1, and WWOX were the most common pathogenic variants, respectively.
- Comorbid conditions are present in 82% of patients, most commonly intellectual disability (70%) and developmental delay (32.1%).
- Movement disorders were present in 12.8% of the rare genetic epilepsies.
- Most of the rare genetic epileptic children (52%) were using more than three anti-seizure drugs.
- After 2 years of treatment, children with rare epilepsy in follow-up have increased developmental delay.

2 | METHODS

Patients diagnosed with rare epilepsy were evaluated in nine tertiary universities and training and research hospitals in Turkey. After obtaining the necessary permission from the ethics committee of the University of Health Sciences at Dr Behçet Uz Children's Training and Research Hospital, the patient data were requested to be processed in the case report form.

Genetic analysis was performed in children presenting with recurrent prolonged (10 min) febrile seizures; febrile

or afebrile status epilepticus (30 min); or with clusters of two or more febrile or afebrile seizures within a 24-h period, early-onset epileptic encephalopathy (EE), and drug-resistant epilepsy. Because genetic testing was done before the study was planned, different analyzes were performed at each center: for example, sequence-comparative genomic hybridization (aCGH), NGS, gene panel, or WES performed according to patients' phenotypes or accessibility of tests.

The collected clinical data included age of seizure onset, seizure types, and frequency of seizures, the number of antiseizure medications (ASM), best responded ASM, general and neurological examination results and family history demographics, clinical findings, electroencephalographies (EEG), neuroimaging studies, and comorbidities. The neuromotor developmental stages were examined yearly. The neuromotor development of children younger than 6 years of age was evaluated with the Denver Developmental screening test. To investigate the clinical factors that most influence the prognosis of neuromotor development, we classified the developmental status into four stages (normal, mild, moderate, and severe), and statistically compared with the following clinical variables, that is, seizure onset type (focal/generalized), comorbidity (+/−), medication number, multiple seizure types (+/−), seizure frequency (daily/weekly/monthly), age at diagnosis of epilepsy, and duration of epilepsy. Developmental stages were classified according to the results of the developmental test.

The concomitant comorbid diseases were noted. Epilepsy syndromes were diagnosed and classified according to the criteria of the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) 2022.[5,6] Patients lacking characteristics of a specific epilepsy syndrome were considered unclassified epileptic encephalopathies. Patients with an identified cause of epilepsy were excluded, including metabolic, infectious, immune, or structural etiology. At least a 50% reduction in seizure frequency after initiation of drug therapy was evaluated as a good response to treatment. Families determined the frequency of seizures by keeping a seizure diary. The physician-in-charge individually estimated the best responded ASM from their experiences.

2.1 | Statistical analysis

Statistical analyzes were performed using the SPSS 21.0 software program for Windows. The results were evaluated within the 95% confidence interval, and the $p < .05$ value was considered significant. Descriptive statistics for categorical variables are percentage and frequency; descriptive statistics for numerical variables are expressed as mean, standard deviation, and minimum (min)–maximum (max) values.

Chi-square analysis was used for categorical variables. A normality test was performed for numerical variables first. Since the number of patients was more than 50, the Kolmogorof–Smirnov test was used as a normality test. As a result of this test, it was understood that the variables did not have a normal distribution; The Mann–Whitney *U*-test was used for the relationship test between two independent groups, the Kruskall–Wallis *H*-test for more than two independent groups, the Wilcoxon Sign Rank test for the relationship test between two dependent groups, and the Friedman test for more than two dependent groups. The binary logistic regression analysis technique (Method: Enter) was used to obtain the effects of the variables on neuro-motor developmental retardation and the probabilities of this effect.

3 | RESULTS

This study included 156 patients from nine tertiary health centers across Turkey. Eighty (51.3%) of the patients were female. The onset of the seizure was 6 months (median). Fifty-nine (37.8%) of the patients had a family history of epilepsy and 59 (37.8%) had consanguinity among their parents.

Gene variants were distributed as follows: 36 patients (23.1%) with SCN1A, 14 (9%) KCNQ2, 10 (6.4%) PCDH19, 6 (3.8%) SCN8A, 5 (3.2%) SLC2A1, and 5 (3.2%) with WWOX. The remaining 80 patients (51.3%) were with other gene variants (KCNT2, KCTD7, PNPO, ALDH7A1, SCN9A, CDKL5, CACNA1A, etc.). There were 1–3 patients from each. According to the ILAE 2022 definition and classification of epilepsy syndromes, 25 (15.4%) patients were classified as self-limited epilepsies, 81 (51.9%) patients as developmental and epileptic encephalopathies (DEE), and 30 (19.2%) patients as etiology-specific syndromes. The clinical characteristics and subclassification of the patients can be seen in Table 1.

Most of the patients were using more than three antiseizure drugs ($n = 81$, 52%). Comorbid conditions are present in 82% of patients, most commonly intellectual disability ($n = 110$, 70%) and developmental delay ($n = 50$, 32.1%). Movement disorders were present in 12.8% ($n = 20$) of the patients. The most common movement disorder was ataxia in patients with pathogenic/likely pathogenic variants in SCN1a (five patients), KCTD7 (three patients), PCDH19 (two patients), NCL2, TSEN, COL4A1, CNTN2, BRAT1, KMT2B, SCAR-10, and RNASEH2B. Two patients with KMT2B and ANO-10 gene variants had dystonia.

In terms of developmental delay in children with rare epilepsy; there was a statistically significant difference

TABLE 1 Clinical characteristics and subclassification of the patients.

Physical examination	
Developmental delay	116 (74.4%)
Microcephaly	80 (51.3%)
Hypotonia	53 (34%)
Normal	37 (23.7%)
Cranial MRI findings	
Corpus callasum involvement	11 (7.1%)
Cerebral atrophy	10 (6.4%)
Cerebral ve cerebellar atrophy	15 (9.6%)
Lissencephaly	2 (1.3%)
PVL	4 (2.6%)
Others	18 (11.5%)
Normal	96 (61.5%)
The presence of two or more types of seizure	87 (55.8%)
Syndromic types	
Developmental and epileptic encephalopathies	81 (51.9%)
Etiology-specific syndromes	30 (19.2%)
Self-limited epilepsies	24 (15.4%)
LGS	6 (3.8%)
SWAS	3 (2%)
PME	3 (1.9%)
SHE	2 (1.3%)
GEE-GTCA	3 (2%)
GE-JAE	1 (0.6%)
GE-JME	1 (0.6%)
LKS	1 (0.6%)
MTS	1 (0.6%)
Developmental and epileptic encephalopathies	
EIDEE	17 (21%)
IESS	27 (33.3%)
Dravet	27 (33.3%)
Non-classified	10 (12.4%)
Self-limited epilepsies	
SeLNE	2 (8.3%)
SelFNIE	4 (16.7%)
SeLIE	6 (25%)
GEFS+	12 (50%)
Etiology-specific syndromes	
PCDH19 clustering epilepsy	10 (33.3%)
KCNQ2-DEE	8 (26.7%)
Glut-1	5 (16.7%)
CDKL5	4 (13.3%)
Pyridoxamine 5′ phosphate deficiency-DEE	1 (3.3%)
Pyridoxine dependent-DEE	2 (6.7%)
The number of drugs used	
Without medication	3 (1.9%)
1 drug	30 (19.2%)
2 drugs	42 (26.9%)
3 drugs or more	81 (52%)
The most efficient drug	
Sodium valproate	31 (19.9%)
Clobazam	15 (9.6%)
Levetiracetam	9 (5.8%)
Topiramate	9 (5.8%)
Carbamazepine	6 (3.8%)
Ketogenic diet therapy	5 (3.2%)
Stiripentol	4 (2.6%)
Comorbidities	128 (82%)
Intellectual disability	110 (70.5%)
Developmental delay	50 (32.1%)
Movement disorders	20 (12.8%)
Autism	11 (7.1%)
Attention deficit hyperactivity disorder	7 (4.5%)
Others	6 (3.9%)

Abbreviations: DEE, developmental and epileptic encephalopathies; GEFS+, genetic epilepsy with febrile seizures plus; LGS, Lennox–Gastaut syndrome; LKS, Landau–Kleffner syndrome; MTS, mesial temporal sclerosis; PME, progressive myoclonic epilepsy; SeLFNIE, self-limited familial neonatal-infantile epilepsy; SeLIE, self-limited infantile epilepsy; SeLNE, self-limited neonatal epilepsy; SWAS, spike–wave activation in sleep.

between their status at the start of treatment, at the end of 1st year of treatment, and at the end of 2nd year of treatment ($p < .001$). Therefore, the neuromotor developmental delay was found to progress with age. In addition, comorbidity, number of ASM, multiple seizure types, seizure frequency, age at diagnosis of epilepsy, and duration of epilepsy all affected the neuromotor developmental status because there were statistically significant differences ($p < .05$), (Table 2). Children with rare epilepsy who had comorbidities are 85.7 times more likely to have neuromotor developmental delay than those who do not. Children with rare epilepsy with neuromotor developmental delay are 6 times more likely to have focal seizure type compared to normal ones.

Variables affecting developmental status were first included in the model one by one (univariate regression); all variables were significant except for neuromotor retardation. However, when all these variables were included in the model together (multivariate regression), only comorbidity and multiple seizure types were significant. Logistic regression analysis was performed with these two variables. Children with rare epilepsy who have

TABLE 2 Statistical analysis results between neuromotor developmental status and variables.

Variables	Statistical test	Category	Statistic	*p*
Seizure onset type	Chi-square	Focal/generalized	7027	.080
Comorbidity		Yes/no	83 254	.000
Number of drugs		Number (1–2)/3+	16 105	.000
Multiple seizure types		Yes/no	12 927	.000
Frequency of seizure	Kruskal–Wallis	Daily/weekly/monthly	14 822	.001
Age at diagnosis of epilepsy	Mann–Whitney	Monthly	13 145	.044
Frequency of seizure		Daily/weekly	406	.317
Frequency of seizure		Daily/monthly	1062	.010
Frequency of seizure		Weekly/monthly	1015	.003
Duration of epilepsy		Year	7945	.000
Neuromotor development (basal) Neuromotor development (1st year) Neuromotor development (2nd year)	Friedman	Normal mild Moderate Sever	45 163	.000
Neuromotor development basal-1st year	Wilcoxon	Normal mild	−5671	.000
Neuromotor development basal-2nd year		Moderate	−4755	.000
Neuromotor development 1st year–2nd year		Sever	−1789	.074

TABLE 3 Logistic regression result of factors affecting neuro-motor development (1st year) status.

Factors	*B*	Standard error	Wald	SD	*p*	Exp (*B*)	95% confidence interval of exp (*B*) Lower	Top
Comorbidity	−2.374	.618	14 770	1	.000	.093	.028	.312
Multipl seizure types	3.094	.498	38 670	1	.000	22.068	8.322	58.517
Model coefficients significance test			**Chi-square**	**df**	***p***			
Omnibus test			96 538	2	.000			

comorbidities have a 10.7 times higher risk of having abnormal neuromotor development than those without. Children with rare epilepsy who have had multiple types of seizures have a 22 times higher risk of their neuromotor development being abnormal than those who have not, Table 3.

4 | DISCUSSION

In this study, the most common SCN1A, KCNQ2, PCDH19, SCN8A, SLC2A1, and WWOX pathogenic/likely pathogenic variants were detected in data obtained from 156 pediatric patients with rare genetic epilepsy collected from 9 medical centers in Turkey, with 128 (82%) of these patients presenting with comorbid conditions. This was a cohort recruited sequentially in routine clinical practice, implying that comorbidities play an important role in children with rare genetic epilepsies.

In a Chinese cohort study most often detected genes were KCNQ2, followed by PRRT2 SCN1A, SCN2A, SPTAN1, and TSC2 in epileptic infants and children. In their study, the positive detection rate was 51.9% using WES (135/260).[7] Zhang et al.[8] performed variant analysis using targeted panel NGS in a cohort and their detection rate was 26%, which was similar to that found by Kothur et al.[9] Early-onset epilepsy had the highest detection rate. Diagnostic yields of targeted panels of 35–265 genes generally ranged between 10% and 48.5%. However, the limited number of genes that can be sequenced for each panel and the need for a continuous updating of the included genes represent major limitations. The reason for the low detection rate may be that they used panel sequencing, which includes fewer genes, instead of WES. When using WES, the diagnostic yield ranged from 11% to 72%.[10–12] We found that the diagnosis rate in our study group varied between 18% and 35% according to the genetic tests used by the center. Because each center requested different tests, there were different numbers of genes in the panels and WES was not applied to all patients in all centers.

Among the priorities for the public health dimension of epilepsy is the necessity for population-based studies on

the prevalence of epilepsy and comorbid conditions.[13] At the most severe end of the complex epilepsy spectrum are early-onset DEE. These are epilepsies characterized by a heterogeneous group of treatment-resistant seizures with significant comorbidity.[14] With NGS available, more gene mutations are being identified that are responsible for the etiology of DEEs. In the present study, 81 (51.9%) of the patients were diagnosed as DEE; 17 of them with early infantile epileptic encephalopathy (EIDEE), 27 of them with infantile epileptic spasm syndrome (IESS), 27 of them with Dravet syndrome, and 10 of them unclassified EE. Similarly to our study, Zhou et al.[15] diagnosed a group of patients with unclassified EEs due to non-specific symptoms. For a given epileptic syndrome, the genetic cause differed and the mutation rate varied from 8.3% to 66.7%. Their study showed that each epileptic syndrome presented more or less specificity in genetic causes, although EEs as a whole presented heterogeneous etiologies. One of the limitations of their study like us the limited sample size. It is hoped that a shift from a syndrome-based system to a more specific definition of clinical phenomenology based on pathophysiology will be made. Similarly, the electroclinical phenotype-based empirical treatment approach will likely be gradually replaced by a treatment approach aimed at correcting neurophysiological dysfunction caused by the genetic defect aimed at reversing or preventing treatment.[16]

In the present study, 78.9% of the patients were using two or more drugs, suggesting that most had drug-resistant epilepsy. More than half of these children had more than one seizure per month. With the development of new technologies such as gene panels and WES in epileptic disorders, the identification of genetic epilepsies has started to accelerate in recent years. Multidisciplinary discussions have proven valuable in difficult diagnostic situations, especially when PM is considered.[17]

In most of the patients in the current study, attempts were made for them to be treated with conventional ASM, while only 5.8% of patients had access to PM treatments (such as the ketogenic diet, and stiripentol). In a multicentre study, there was a treatment change prompted by the genetic diagnosis, but not directly related to known pathophysiological mechanisms. Their findings also highlight that lower age at genetic tests was associated with better outcomes.[18]

Today, people with epilepsy and their caregivers carry restrictions and social burdens in their daily lives. New gene discoveries have proven that PM is necessary, but it is crucial to understand whether the phenotype in epileptic channelopathies is due to loss-of-function or gain mutations in the encoded protein. Likewise, if a new gene is identified, it is essential to understand through what mechanism it may cause disease and then determine the best treatment to reverse the functional defect. However, considering a PM-based approach requires a holistic assessment of the clinician and an in-depth knowledge of the patient's phenotype.[4] In particular, sodium channel blockers have been reported to have variable efficacy in patients with KCNQ2 in infancy, as well as for patients with SCN1A, CDKL5, KCNQ2, STXBP1, and SCN2A mutations. Quinidine may be effective in some patients with migrating focal epilepsy due to KCNT1 mutations in infancy, but not in others.[19–21]

Extensive phenotypic and genetic heterogeneity has been observed in many monogenic epilepsies, meaning that genotype–phenotype correlations are not always straightforward. The same gene and even the same mutation can lead to broad phenotypic variations, and the same epilepsy syndrome can be caused by mutations in different genes.[22] Precision medicine may prove complex, as the same mutation may cause quite different clinical phenotypes; moreover, additional genetic variants may contribute to modifying a phenotype. Again, wide-genome variations or even the epigenome may influence the resulting expression of pathogenic variants.[23]

In our study, we found that the age of onset of epilepsy was lower in children with rare epilepsy and developmental delay. We found that children with rare epilepsy are more likely to have developmental delay if they have frequent seizures, multiple seizure types, use of more than 3 drugs, long-term epilepsy, comorbidity, and focal seizures. The probability of developmental delay was highest (96%) when both multiple seizure types and comorbidities were present. Balagura et al.[24] analyzed the disease course of STXBP1-DEE and found that age at seizure onset correlated with the severity of the developmental outcome. Overall, they did not observe a clear genotype–phenotype correlation. Such studies support the statement that 'polygenic factors might contribute to both epilepsy and cognitive impairment in the same patient' and can eventually inform future dedicated natural history studies and trial designs in patients with childhood epilepsy. Malerba et al.[25] failed to identify a relationship between variant position and seizure offset or cognitive outcome in patients harboring missense variants. However, recurrent variants were associated with overlapping epilepsy features but also variable evolution regarding the intellectual outcome. In our study, the genotype–phenotype correlation was found in most of the patients, particularly those with Dravet syndrome and SCN1a mutation, and those with KCNQ2 mutations while we found a genotype–phenotype mismatch in some of them. Scala et al.[26] reported that genotype–phenotype correlations may appear substantial in selected cases (e.g., patients with Dravet syndrome caused by SCN1A mutations), but they are generally quite indefinite due to the genetic and allelic heterogeneity, similar to our result.

Despite the dramatic increase in orphan drug development over the last 10 years for rare epilepsies, the number of approved drugs is limited to very few syndromes such as Dravet syndrome, Lennox–Gastaut syndrome, and infantile epileptic spasm syndrome. Hypotheses and exploratory clinical studies based on the pathophysiology of causative gene mutation, including animal models, are needed for more effective treatment in rare epilepsies.[27] Investigating the molecular mechanisms of epilepsy has changed our approach to epileptic patients, but the pathophysiology of diseases may be more complex than we can model, as different concomitant genetic variants, epigenetics, or the environment may modulate phenotypes in unintelligible. Patients are still diagnosed late today, increasing the need for clinicians to better define phenotyping. Therefore, newer and standardized tools of phenotyping will also be needed, the human phenotype ontology with a standardized vocabulary can help with this. Early diagnosis and early and non-invasive treatment remain hopeful for improving patients' quality of life and learning curve.[4] A thorough electro-clinical characterization of the patient is essential to guide the choice of the best genetic test and provide relevant support in genetic data interpretation. In addition, regular clinical evaluations significantly improve this complex diagnostic process.[26]

Moreover, different epilepsy syndromes are sometimes associated with the same genetic variant or variants in different genes can result in a similar phenotype, and the complexities of the genotype–phenotype correlation increase the difficulty of accurate clinical diagnosis. In a study in China among the 135 positive/likely positive probands, 106 patients had more than two phenotypes, and 67 patients had more than three phenotypes indicating that epilepsy has a highly heterogeneous clinical phenotype.[7] However, the ILAE 2022 syndrome classification was not used in this study. Rochtus et al.[28] evaluated the yield of systematic analysis and/or reanalysis of WES data from a cohort of well-phenotyped pediatric patients with epilepsy and suspected but previously undetermined genetic etiology. They identified pathogenic or likely pathogenic variants in 40% of their study participants. They illustrated the dynamic nature of genetic diagnosis over time, with analysis and in some cases reanalysis of exome data leading to the identification of disease-associated variants among participants with previously nondiagnostic results from a variety of clinical testing strategies. We also planned to reevaluate the data of our patients every year. Due to the heterogeneity of epileptic disorders, the selection of the most appropriate genetic test to be performed on each patient is of great importance to increase the diagnostic yield. This selection should begin with the pediatric neurologist harmonizing the patient's history, electro-clinical features, and neuroimaging findings. Cytogenetic analysis by Array-CGH and, in selected cases, FISH may be helpful in syndromic patients. Instead, MLPA can be performed to exclude possible deletions of genes already associated with distinctive epileptic phenotypes. In non-syndromic patients, NGS-based testing plays a primary role. Despite improved interpretation of test results from NGS-based techniques, WES is currently a remarkable diagnostic tool in patients with epilepsy without a genetic diagnosis. Perhaps future WGS studies will explain unresolved cases, allowing interpretation of changes in non-coding regions that are currently undecipherable.[26]

It has been reported that early-onset epilepsy is accompanied by a wide variety of comorbidities. Usually, these morbidities are collected in a single patient. Rather than being separate conditions, they are all combined expressions of developmental brain disorders, including seizures. Rather than viewing epilepsy as comorbidities of disease and other features, approaching early-life epilepsies as part of the spectrum of neurodevelopmental disorders (NDD) may have beneficial implications for multidisciplinary models of care, forward-looking guidance, and counseling to parents At the same time, it may be important for each country to determine the data of its patients in terms of revealing the geographical distribution and socioeconomic effects of these rare genetic epilepsies.

An important issue is that epilepsy is a frequent feature of NDDs, but little is known about genetic differences between NDDs with and without epilepsy. Heyne et al.[29] compared NDD with and without epilepsy, they found the age of recruitment and severity of intellectual disability to be associated with epilepsy. They demonstrated the benefit of accurate genetic diagnosis in NDD with epilepsy. Another seminal paper by the Epi25Consortium[30] showed that compared to controls, individuals with any type of epilepsy carried an excess of ultra-rare, deleterious variants in constrained genes and in genes previously associated with epilepsy with the strongest enrichment in individuals with DEEs. Notably, this paper did also show that inhibitory GABAA receptor genes were enriched for missense variants, with relevant pathogenetic implications. Studying rare genetic variations involving severe to milder electroclinical syndromes of epilepsy can help researchers to better understand the extent of phenotypic pleiotropy and variable expressivity that could inform treatment strategies.

To obtain earlier and more appropriate treatment strategies, clinicians need to understand the effects of specific genetic causes on pathophysiology, natural history, comorbidities, and treatment options. Overall, there is insufficient evidence to guide ASM choices in genetic epilepsies. The effectiveness of the ketogenic diet in glucose transporter deficiency syndrome (GLUT1DS) is an excellent example of how the knowledge of the genetic defect underlying an epileptic disorder may suggest a specific

treatment strategy. The correction of this deficiency in patients with GLUT1DS results in the improvement of both epilepsy and comorbidities.[31]

Precision medicine remains available to only a very small number of patients with monogenic epilepsies and can target only a fraction of true functional defects. Some genetic mutations activate epileptogenesis. Other genes have functional consequences on excitability, either through loss of function or gain of effects, and they have adverse treatment effects. Among the promising developments is gene manipulation with mRNA targeting, some of which are in early clinical development.[32] The fact is that key processes in epileptogenesis are under the control of miRNAs. In our previous study, we found that ha-miR-146a-5p, has-miR-138-5p, and has-miR-187-3p were downregulated in children with EE. This made us think that more studies are needed to prove that miRNAs could contribute to the development of PMs.[33] This opens the way to N-of-1 trials, which will hopefully be the road of the next few years not only in oncology but also in epileptic patients.[23] Dravet syndrome results from heterozygous loss of function variants in SCN1A encoding a voltage-gated sodium channel involved in the generation and propagation of the action potential.[34] According to this pathogenic model, sodium channel-blocking drugs should be avoided in SCN1A-associated Dravet syndrome because these drugs it is usually ineffective or can worsen seizures.[35,36] These patients may instead benefit from new therapeutic strategies developed in recent years, such as ASOs and selectively activating peptides that restore SCN1A mRNA. Nav1.1 channel in inhibitory interneurons.[37–40] Vinpocetine, an alkaloid that amplifies GABA-evoked currents, has been used successfully to treat LGS caused by the GABRB3 mutation.[41] The novel compounds MPX-004 and MPX-007 have been developed to selectively block NMDA receptors containing the NR2A subunit in patients with a gain of function mutations in GRIN2A.[42]

Understanding the natural history of the disease, predicting long-term consequences, and preventive strategies are very important to develop disease-modifying treatments. We can think that many factors contribute to the course of the disease, including brain development, specific gene abnormality, and associated neurophysiological dysfunction, changes in gene expression over time, the role of modifier genes, as well as the clinical frequency of seizure and behavioral disorders.[7]

Despite the complexity of genetic testing in epileptic disorders, every effort should be made to arrive at a definitive genetic diagnosis. Genetic characterization of patients with epilepsy plays a crucial role in choosing the best therapeutic options and improving patient care. Collaboration between geneticists and pediatric neurologists still represents the cornerstone of genetic diagnosis in epilepsy. The interdisciplinary approach and international cooperation will certainly enable us to achieve further significant advances in epilepsy research in the future. Early treatment will allow the minimization of the effects of epilepsy on cognitive performances and possibly partially reverse the inevitable cognitive decline.[26]

5 | CONCLUSION

In this cohort, SCN1A, KCNQ2, PCDH19, SCN8A, SLC2A1, and WWOX were the most common pathogenic variants, respectively. Comorbid conditions are present in 82% of patients, most commonly intellectual disability (70%) and developmental delay (32.1%). Movement disorders were present in 12.8% of the rare genetic epilepsies. Most of the rare genetic epileptic children (52%) were using more than three anti-seizure drugs. After 2 years of treatment, children with rare epilepsy in follow-up have increased developmental delay. The most important variables affecting developmental delay were found to be multiple seizure types and comorbidity. Since a complete cure cannot be achieved in the vast majority of these patients, further studies with collaboration among centers might help improve therapeutic decisions and personalized treatment methods.

AUTHOR CONTRIBUTIONS

All authors whose names appear on the submission: (1) Made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work. (2) Drafted the work or revised it critically for important intellectual content. (3) Approved the version to be published. (4) Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest in our study and the material described is not under publication or consideration for publication elsewhere.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

INFORMED CONSENT

Informed consent form obtained from participants. Additional informed consent was obtained from all individual

participants for whom identifying information is included in this article. We confirm giving permission to reproduce material from other sources. There is no clinical trial registration.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

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Test yourself

1. Why networking is necessary for rare epilepsies?
   A. Collaboration
   B. Research
   C. Resource development
   D. Development of individualized treatments
   E. Creation of new treatment modalities
   F. All of the above
2. Why is it important to know the incidence and prevalence of rare epilepsies?
   A. Most of them are drug-resistant epilepsy
   B. The growth, breadth, and complexity of rare epilepsies underscore the importance of measuring the incidence and prevalence
   C. Concomitant comorbid condition in more than half
   D. They create both psychosocial burdens on families and health workers
   E. They create an economic burden on society and the country
   F. All of the above
3. Why precision medicine and new treatment studies are needed for rare epilepsies?
   A. Since a complete cure cannot be achieved in the vast majority of these patients
   B. For the development of more cost-effective treatments
   C. To improve quality of life
   D. To increase life expectancy
   E. To reduce hospitalizations
   F. All of the above

Answers may be found in the supporting information