Analysis of Genetic and Clinical Features in Pediatric Drug-Resistant Epilepsy: Postprint

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Abstract

Background Currently, drug-resistant epilepsy (DRE) in children accounts for approximately 30% of pediatric epilepsy cases and is often complicated by mental retardation, significantly impacting patients' quality of life. Therefore, the diagnosis and treatment of DRE remains a major challenge in neurology.

Objective To analyze the genetic characteristics and clinical features of DRE in children and provide a theoretical basis for clinical genetic testing.

Methods We retrospectively selected 95 children with DRE who were hospitalized at Hebei Children' s Hospital from January 2020 to December 2022 and underwent comprehensive genetic testing. Based on the genetic test results, they were divided into a gene mutation-positive group (44 cases) and a gene mutation-negative group (51 cases). General data (including gender, age of onset, medication usage, history of febrile seizures, family history of epilepsy, etc.), clinical features (seizure types, epilepsy syndromes, developmental status), and auxiliary examinations [genetic testing, video electroencephalogram (VEEG), neuroimaging studies] were collected to analyze the genetic etiology and clinical features of DRE.

Results Among the 95 children with DRE, 55 were male (57.9%) and 40 were female (42.1%). The median age of onset was 0.50 (1.00, 4.00) years, and the median number of antiepileptic drugs used was 3 (2, 4). The age of onset in the gene mutation-positive group was significantly younger than that in the gene mutation-negative group (Z=-5.322, P=0.001). No statistically significant differences were found between the two groups in gender, history of febrile seizures, family history of epilepsy, or number of medications used (P>0.05). Epilepsy syndromes were diagnosed in 38 children (40.0%), with 76.3% (29/38) having onset in the neonatal or infantile period. The proportion of epilepsy syndromes was significantly higher in the gene mutation-positive group than in the gene mutation-negative group (^{2}=12.065, P=0.001). Clinical seizure types were diverse, with the most common being two or more seizure types (52.6%,

50/95), followed by single focal seizures (33.7%, 32/95). No statistically significant difference in seizure types was observed between the two groups (^{2}=2.920, P=0.404). Developmental screening was completed in 57 children, among whom 43 (75.4%) developed varying degrees of developmental delay after onset, with 33 (76.7%) showing global developmental delay. The proportion of developmental delay was significantly higher in the gene mutation-positive group than in the gene mutation-negative group (^{2}=5.728, P=0.017). Variant genes were detected in 44 children, with a positive detection rate of 46.3%, predominantly ion channel variants, with SCN1A being the most common single-gene mutation. VEEG abnormalities were observed in 90 children (94.7%), mainly showing focal epileptiform discharges. The proportion of hypsarrhythmia was significantly higher in the gene mutation-positive group than in the gene mutation-negative group (^{2}=7.425, P=0.006). Structural etiologies were identified in 25 children (26.3%), including 12 cases in the gene mutation-positive group and 13 cases in the gene mutation-negative group. No statistically significant difference in structural etiologies was found between the two groups (^{2}=0.039, P=0.844).

Conclusion Genetic factors are an important cause of DRE in children. Young age of onset and developmental delay suggest an association with genetic etiologies. Early comprehensive genetic testing should be actively pursued to facilitate early diagnosis of DRE and enable precision treatment.

Full Text

Clinical Features and Genetic Analysis of Drug-Resistant Epilepsy in Children

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Abstract

Background: Drug-resistant epilepsy (DRE) affects approximately 30% of children with epilepsy and is often associated with mental retardation, significantly impacting quality of life. The diagnosis and treatment of DRE remain major challenges in neurology. **Objective:** To analyze the genetic characteristics and clinical features of DRE in children to provide a theoretical basis for clinical genetic testing. **Methods:** We retrospectively enrolled 95 children with DRE who were hospitalized at Hebei Children' s Hospital between January 2020 and December 2022 and underwent genetic testing. Based on genetic test results, patients were divided into a gene mutation-positive group (44 cases) and a

gene mutation-negative group (51 cases). We collected general data (including gender, age of onset, medication use, history of febrile convulsions, family history of epilepsy, etc.), clinical features (seizure types, epilepsy syndromes, developmental status), and auxiliary examinations [genetic testing, video electroencephalography (VEEG), neuroimaging] to analyze the genetic etiology and clinical characteristics of DRE. **Results:** Among the 95 children with DRE, 55 (57.9%) were male and 40 (42.1%) were female, with a median age of onset of 0.50 (1.00, 4.00) years and a median of 3 (2, 4) antiepileptic medications used. The gene mutation-positive group had a younger age of onset than the mutation-negative group (Z=-5.322, P=0.001). No statistically significant differences were observed between groups in gender, history of febrile seizures, family history of epilepsy, or number of medications used (P>0.05). Epilepsy syndromes were diagnosed in 38 cases (40.0%), with 76.3% (29/38) having onset in the neonatal or infantile period. The proportion of epilepsy syndromes was significantly higher in the gene mutation-positive group than in the mutation-negative group (^{2}=12.065, P=0.001). Clinical seizure types were diverse, with 52.6% (50/95) having two or more seizure types, followed by single focal seizures in 33.7% (32/95). No significant difference in seizure types was found between groups (^{2}=2.920, P=0.404). Developmental screening was completed in 57 children, among whom 43 (75.4%) showed varying degrees of developmental delay after seizure onset, with 76.7% (33/43) exhibiting global developmental delay. The proportion of developmental delay was higher in the gene mutation-positive group (^{2}=5.728, P=0.017). Pathogenic or likely pathogenic variants were detected in 44 children (46.3% detection rate), predominantly involving ion channel-related mutations, with SCN1A being the most common single-gene mutation. VEEG abnormalities were observed in 90 children (94.7%), mainly showing focal epileptic discharges. The gene mutation-positive group had a higher proportion of hypsarrhythmia than the mutation-negative group (^{2}=7.425, P=0.006). Structural etiology was identified in 25 children (26.3%), with no significant difference between groups (^{2}=0.039, P=0.844). **Conclusion:** Genetic factors represent an important etiology of DRE in children. Young age of onset and developmental delay suggest a genetic etiology, and early genetic testing should be actively pursued to facilitate early diagnosis and precision treatment of DRE.

Keywords: Drug-resistant epilepsy; Child; Genetics; Genetic testing; Epileptic syndromes; Clinical characteristics; Global developmental delay

Introduction

Epilepsy is a common chronic neurological disorder characterized by recurrent seizures caused by transient abnormal neuronal activity. While most seizure disorders can be controlled with antiepileptic medications, drug-resistant epilepsy (DRE) is defined as failure to achieve sustained seizure freedom despite adequate trials of two tolerated, appropriately chosen, and correctly used antiepileptic

drug regimens [1]. DRE affects approximately 10-30% of children with epilepsy [2]. According to the 2017 International League Against Epilepsy (ILAE) classification of epilepsy etiologies [3], although epilepsy can be caused by structural, metabolic, immune, and other factors, most patients with DRE are believed to have underlying genetic factors. However, due to the high cost of genetic screening, many families decline testing because of financial pressure, making it difficult to implement universal genetic screening for all children with DRE. Consequently, research on which specific subgroups of DRE patients should undergo genetic testing remains limited. This retrospective study analyzed the distribution of genetic etiologies and associated clinical manifestations in children with DRE to provide guidance for genetic screening in this population.

Methods

Study Design and Participants We retrospectively enrolled children with DRE who were hospitalized in the Department of Neurology at Hebei Children' s Hospital between January 2020 and December 2022 and completed genetic testing. The inclusion criteria were: (1) fulfillment of the 2010 ILAE diagnostic criteria for DRE; (2) complete medical records with available genetic testing and VEEG examinations. Exclusion criteria included: (1) pseudo-drug-resistant epilepsy events due to irrational medication use; (2) poor compliance (irregular medication intake or self-adjusted dosages) resulting in subtherapeutic drug levels; and (3) severe systemic diseases such as congenital heart disease. The study was approved by the Ethics Committee of Hebei Children' s Hospital (approval number: 202103), and informed consent was obtained from all guardians.

Data Collection We reviewed the hospital's electronic medical record system to collect general data (including gender, age of onset, medication use, history of febrile convulsions, family history of epilepsy), clinical features (seizure types, epilepsy syndromes, developmental status), and auxiliary examinations [genetic testing, video electroencephalography (VEEG), neuroimaging].

Genetic Testing Peripheral blood samples were collected from patients and their family members for DNA extraction and sent to a third-party genetic testing company for trio whole-exome sequencing. The pathogenicity of genetic variants was evaluated according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines [4]. Based on genetic test results, patients were divided into a gene mutation-positive group (44 cases) and a gene mutation-negative group (51 cases) for comparative analysis of clinical characteristics.

Diagnostic Criteria The diagnosis of DRE was established according to the 2010 ILAE criteria [1]: failure to achieve seizure freedom for a duration equal to three times the longest pre-treatment interseizure interval or one year (whichever was longer) despite adequate trials of at least two tolerated antiepileptic med-

ications, appropriately selected for the seizure type(s) and correctly used as monotherapy or in combination.

The diagnostic criteria for infantile epileptic spasm syndrome (IESS) included: (1) fulfillment of IESS diagnostic standards [5]—predominant spasm seizures often occurring in clusters, interictal VEEG showing hypsarrhythmia or multifocal/focal discharges, onset between 1 and 24 months of age, and developmental regression following spasm onset; and (2) fulfillment of DRE diagnostic criteria.

Developmental screening was performed using age-appropriate scales: the Gesell Developmental Scales (GDS) for children aged 0-6 years, assessing five domains (adaptive behavior, gross motor, fine motor, language, and personal-social skills) with developmental quotient (DQ) scores—DQ <75 indicating developmental delay; and the Wechsler Intelligence Scale for Children (WISC) for ages 6-16 years, evaluating four indices (verbal comprehension, perceptual reasoning, working memory, processing speed) and full-scale IQ, with IQ <70 indicating intellectual disability.

Global developmental delay (GDD) was defined as significant delays in two or more developmental domains (gross motor, fine motor, language, cognition, social skills, and adaptive functioning) in children under 5 years who failed to achieve expected developmental milestones [6]. Intellectual disability was diagnosed in children over 5 years.

Epilepsy syndromes were defined according to the 2022 ILAE classification as a group of clinical and electrographic phenotypes with characteristic features and often specific etiologies (structural, genetic, metabolic, immune, or infectious) [5]. Syndromes were categorized by age of onset into neonatal/infantile onset, childhood onset, variable age onset, and idiopathic generalized epilepsies.

Statistical Analysis Statistical analysis was performed using SPSS 26.0 software. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared between groups using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages, with comparisons made using the ^{2} test or Fisher' s exact test. A P-value <0.05 was considered statistically significant.

Results

General Characteristics During the study period, 102 children were initially identified. After excluding 4 cases with poor medication compliance and 3 cases that did not achieve therapeutic drug concentrations, 95 children with DRE were included in the final analysis. The cohort comprised 55 males (57.9%) and 40 females (42.1%), with a median age of onset of 0.50 (1.00, 4.00) years and a median of 3 (2, 4) antiepileptic medications used. The gene mutation-positive group had a significantly younger age of onset compared to the mutation-negative group (Z=-5.322, P=0.001). No statistically significant differences were

observed between groups in gender distribution, history of febrile seizures, family history of epilepsy, or number of medications used (P>0.05) .

Clinical Features Epilepsy Syndromes: A total of 38 children (40.0%) were diagnosed with specific epilepsy syndromes, with 76.3% (29/38) having onset in the neonatal or infantile period. The proportion of epilepsy syndromes was significantly higher in the gene mutation-positive group than in the mutation-negative group (^{2}=12.065, P=0.001). Among these, 26 cases were classified as developmental and epileptic encephalopathy (DEE), including 10 cases of IESS, 6 cases of Dravet syndrome, 5 cases of early-infantile DEE, and 1 case of Lennox-Gastaut syndrome. Three cases were etiology-specific epileptic encephalopathies associated with KCNQ2, CDKL5, and PCDH19 variants. Nine cases (23.7%) had childhood-onset epilepsy syndromes, including 4 cases of Lennox-Gastaut syndrome, 1 case of febrile infection-related epilepsy syndrome (FIRES), 1 case of self-limited epilepsy with centrotemporal spikes (SeLECTS), and 3 unclassified epileptic encephalopathies.

Seizure Types: Clinical seizure types were diverse, with 52.6% (50/95) of children experiencing two or more seizure types (most commonly focal seizures combined with other types), followed by single focal seizures in 33.7% (32/95), single generalized seizures in 8.4% (8/95), and single spasm seizures in 5.3% (5/95). No significant difference in seizure type distribution was found between the two groups (^{2}=2.920, P=0.404) .

Developmental Status: Developmental screening was completed in 57 children, among whom 43 (75.4%) showed varying degrees of developmental delay or intellectual disability after seizure onset. Global developmental delay was observed in 76.7% (33/43), intellectual disability in 13.9% (6/43), and language delay in 9.3% (4/43). The proportion of developmental delay was significantly higher in the gene mutation-positive group (87.5%, 28/32) compared to the mutation-negative group (60.0%, 15/25) (^{2}=5.728, P=0.017).

Auxiliary Examinations Genetic Testing: All enrolled children underwent trio whole-exome sequencing. Pathogenic or likely pathogenic variants were identified in 44 children (46.3% detection rate), including 23 (52.3%) de novo mutations and 21 (47.7%) inherited variants. A total of 30 different gene variants were detected, comprising 29 single-gene variants and 1 chromosomal abnormality. Classification by encoded protein function revealed that ion channel-related genes were most prevalent (52.3%, 23/44), with voltage-gated sodium channels being the most common subtype (47.8%, 11/23). SCN1A was the most frequent single-gene mutation .

VEEG Findings: VEEG abnormalities were observed in 90 children (94.7%), predominantly showing epileptiform discharges such as spike/sharp-and-slow wave complexes, spikes, and sharp waves. Classification of EEG findings revealed abnormal background activity in 35 cases (36.8%), generalized discharges in 23 cases (24.2%), focal discharges in 46 cases (48.4%), and special EEG

phenomena in 21 cases (22.1%). No significant differences were found between groups in background activity, generalized discharges, or focal discharges (P>0.05). However, the gene mutation-positive group showed a significantly higher proportion of hypsarrhythmia compared to the mutation-negative group (P<0.05) .

Neuroimaging: All 95 children underwent brain magnetic resonance imaging (MRI), with 38.9% (37/95) showing abnormal signals. Structural etiology was identified in 25 children (26.3%), including 12 in the gene mutation-positive group and 13 in the mutation-negative group, with no significant difference between groups (^{2}=0.039, P=0.844) . Structural abnormalities included tuberous sclerosis, cortical dysplasia, multiple intracranial abnormal signals, encephalomalacia and gliosis, hemispheric atrophy, and cavernous hemangioma.

Discussion

Despite the continuous development of new antiepileptic medications, the prevalence of DRE remains at approximately 30% and is frequently associated with intellectual disability, psychiatric comorbidities, and reduced quality of life [7]. Genetic factors represent a common cause of DRE in children, and early genetic testing can help determine appropriate treatment strategies and improve prognosis. Therefore, investigating the clinical features of DRE children with positive genetic findings is crucial for clinical practice.

Our study revealed a genetic mutation detection rate of 46.3% (44/95) in children with DRE, which is comparable to the 55.5% (25/45) reported by Kocaaga et al. [8]. Ion channel-related gene mutations were the most common finding, including SCN1A and KCNQ2 variants, consistent with observations by Liu et al. [9]. Other identified genes included enzyme regulators such as CDKL5, cell metabolism and signal transduction components exemplified by FGF12, and cell adhesion molecules like PCDH19. Notably, we identified one child with chromosomal copy number variation (13.6 Mb deletion at 18q22.1q23) presenting with DRE, microcephaly, and comprehensive developmental disability [10]. Copy number variations reportedly account for approximately 10% of genetic epilepsy cases [11]. Additionally, three children harbored mitochondrial gene mutations (POLG, MT-TL1, and TLDNM1L), all of which have been documented in the literature [12-14]. Mitochondrial-related epilepsy exhibits complex pathogenesis, multiple seizure types, and is mostly drug-resistant, often accompanied by multisystem involvement and poor prognosis. Multiple studies have demonstrated the transformative potential of definitive genetic diagnosis in clinical management [15-19]. When treatment is individualized based on genetic findings, 44-80% of patients experience seizure reduction or even freedom, underscoring the profound impact of early genetic testing on improving outcomes in epilepsy.

Regarding demographic characteristics, no gender difference was observed between groups; however, the gene mutation-positive group had a significantly

earlier age of onset than the negative group ($P<0.05$), consistent with findings by Bayat et al. [20]. A prospective Scottish study similarly found that epilepsy onset before 6 months of age was significantly associated with a genetic diagnosis [17]. Song et al. [21] also demonstrated that genetic variants are the leading cause of epilepsy in infants younger than 6 months. Furthermore, age at seizure onset has been identified as a predictor of DRE, with younger onset age carrying higher risk for drug resistance [22]. Collectively, these findings suggest that younger age of onset in DRE children is strongly associated with genetic etiologies.

Clinically, 40% (38/95) of DRE children were diagnosed with specific epilepsy syndromes. Previous studies have reported that approximately 54% of epilepsy patients can be diagnosed with a syndrome before age 3 years [23]; the slightly lower proportion in our study may be related to the wider age range of enrolled patients. The significantly higher rate of epilepsy syndrome diagnosis in the gene mutation-positive group ($P<0.05$) suggests an association between genetic etiology and recognizable epilepsy syndromes. Most patients (76.3%) had neonatal or infantile onset, with IESS being most common, followed by Dravet syndrome. All six Dravet syndrome patients in our cohort harbored SCN1A variants, consistent with previous reports of >80% association [24]. Regarding seizure types, 52.6% (50/95) of DRE children had two or more seizure types, with single focal seizures being the next most common pattern. No significant difference in seizure type distribution was observed between groups ($P>0.05$), aligning with previous research by Lin et al. [25] showing that multiple seizure types are a risk factor for developing DRE. Concerning developmental outcomes, developmental screening revealed that 75.4% of evaluated children had varying degrees of psychomotor developmental delay or regression after seizure onset, with a significantly higher rate of developmental abnormalities in the gene mutation-positive group (87.5%) compared to the negative group ($P<0.05$). These findings are consistent with Bayat et al. [20], who reported associations between underlying genetic factors, younger age of onset, specific epilepsy syndromes, and intractable seizures with developmental delay. With advances in genomics, over 400 genes have been implicated in developmental disorders and epilepsy [26].

Zhang et al. [27] reported a VEEG positivity rate of approximately 87.6% in DRE patients. Our study found a higher abnormal VEEG rate of 94.7%, possibly because our cohort was restricted to children while the previous study had no age limitation. Abnormal VEEG predominantly showed epileptiform discharges such as spike/sharp-and-slow wave complexes, spikes, and sharp waves, with focal discharges being most common—important for localizing seizure onset. A minority showed special EEG phenomena such as hypsarrhythmia, multifocal, and migratory focal discharges, which often indicate greater treatment difficulty. The higher proportion of hypsarrhythmia in the gene mutation-positive group may be attributed to the higher prevalence of IESS in this group, though larger samples are needed for confirmation.

Structural brain abnormalities represent another important etiology of DRE. Twelve children in the gene mutation-positive group had coexisting structural etiologies, which may be causally related to genetic variants (e.g., TSC gene variants in tuberous sclerosis) or represent independent epileptogenic factors. In the gene mutation-negative group, 13 children had structural etiologies, predominantly cortical dysplasia and hippocampal sclerosis/lesions, with no significant difference between groups ($P>0.05$). Some patients may be candidates for surgical treatment based on imaging findings; previous studies have shown that 50-60% of children with positive MRI findings can achieve seizure freedom after epilepsy surgery, with 20-30% experiencing seizure reduction [28]. However, 15-30% of refractory focal epilepsies show negative MRI findings without clear lesions [29]. Recent studies demonstrate that PET-MRI fusion imaging can effectively increase the positive detection rate by combining PET' s metabolic sensitivity with MRI' s superior spatial resolution, providing integrated structural, metabolic, and functional information to better localize epileptogenic foci [30].

This study has several limitations. First, as a single-center study with a relatively small sample size, multi-center expansion is warranted. Second, we only investigated the genetic characteristics and clinical manifestations of DRE without longitudinally examining the impact of genetic testing on treatment decisions. Future prospective studies should follow patients to assess changes in seizure outcomes after treatment adjustments based on genetic findings.

In conclusion, 46.3% of children with DRE have an underlying genetic etiology, with ion channel-related genes representing the primary variant type. The gene mutation-positive group demonstrated younger age of onset, higher rates of epilepsy syndromes, greater developmental delay, and increased prevalence of hypsarrhythmia on VEEG compared to the mutation-negative group. These findings suggest that genetic testing should be actively pursued in DRE children with these clinical features. Early etiological diagnosis not only helps families understand the condition and prepare for long-term standardized treatment but also enables clinicians to develop safe and effective, etiology-targeted strategies involving medications, surgery, and precision therapy, thereby improving seizure control and developmental outcomes.

Author Contributions: ZUO Ranran contributed to study conception, data collection, figure preparation, and manuscript writing. SUN Suzhen was responsible for quality control and revision of the manuscript and takes overall responsibility for the work.

Conflict of Interest: The authors declare no conflict of interest.

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Tables

Note: Figure translations are in progress. See original paper for figures.