Postprint of "Analysis of High-Risk Factors for Drug-Resistant Epilepsy in Children and Study on Its Impact on the Development of Different Functional Brain Regions in Pediatric Patients"

Authors: Liu Yu, Kong Lina, Du Kaixian, Guan Jing, Chen Hao, Li Lin, Li Xiao, Song Panpan, Peng Yanhua, Du Kaixian

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Abstract

Background: Drug-resistant epilepsy (DRE) in children is a common neurological disorder in childhood. Approximately one-third of pediatric patients with epilepsy fail to achieve sustained seizure freedom despite treatment with two appropriately chosen and well-tolerated antiseizure medications. Long-term and recurrent seizures or status epilepticus can exert severe effects on cognition, memory, quality of life, psychosocial status, and overall growth and development in children. At the same time, DRE causes multiple irreversible impairments to the developing nervous system in children. Objective: To investigate the high-risk factors for DRE in children and their impact on the development of different functional domains. Methods: A total of 250 newly diagnosed children with epilepsy admitted to the Pediatric Neurology Department of the Third Affiliated Hospital of Zhengzhou University between January 2023 and October 2024 were enrolled. According to their response to pharmacological treatment, they were divided into a drug-resistant group (n=94) and a non-drug-resistant group (n=156). In addition, 80 age-matched healthy children who underwent routine health examination and were assessed with the Chinese version of the Griffiths Mental Development Scales (GDS-C) during the same period were recruited as the normal control group. Clinical data and GDS-C assessment results were collected. The GDS-C covered six functional domains: locomotor, personal-social, language, eye-hand coordination, performance, and practical reasoning. Statistical analysis was performed using SPSS 25.0. Multivariate stepwise logistic regression analysis was used to explore high-risk factors for DRE in children. Receiver operating characteristic (ROC) curves were plotted for individual high-risk factors and the combined indicator to predict pediatric DRE. Results: Significant differences were found between the drug-resistant and

non-drug-resistant groups in terms of body weight, age at onset, precipitating factors of first seizure, change in seizure type, genetic etiology, structural etiology, unknown etiology, seizure duration before treatment, seizure frequency before treatment, status epilepticus, response to the first antiseizure medication, developmental delay, history of febrile seizures, birth history, fibrinogen, blood ammonia, ceruloplasmin, vitamin D, cranial MRI findings, initial EEG findings, EEG findings after 6 months of treatment, multifocal epileptiform discharges, and chromosomal and genetic testing (all P<0.05). Multivariate stepwise logistic regression analysis showed that poor response to the first antiseizure medication (OR=18.928, 95%CI=8.392-42.693, P<0.001), longer seizure duration before treatment (OR=1.089, 95%CI=1.006-1.180, P=0.036), developmental delay (OR=3.415, 95%CI=1.504-7.754, P=0.003), and multifocal epileptiform discharges (OR=5.265, 95%CI=2.335-11.873, P<0.001) were high-risk factors for DRE in children. ROC curve analysis showed that the area under the ROC curve (AUC) of the combined indicator for predicting pediatric DRE was 0.920 (95%CI=0.887-0.953), with an optimal cutoff value of 0.316, sensitivity of 0.904, and specificity of 0.801. Comparison of developmental quotients in the six functional domains among the control group, drug-resistant group, and non-drug-resistant group revealed statistically significant differences (all P<0.05). The developmental quotients of locomotor, personal-social, language, eye-hand coordination, and performance domains in the non-drug-resistant group were higher than those in the drug-resistant group but lower than those in the control group (P<0.05). Conclusions: Poor response to the first antiseizure medication, longer seizure duration before treatment, developmental delay, and multifocal epileptiform discharges are high-risk factors for DRE in children. The constructed predictive model based on combined indicators has clinical reference value; children with DRE exhibit significant developmental delay across multiple functional domains.

Full Text

Abstract

Background: Drug-resistant epilepsy (DRE) in children is a common neurological disorder during childhood. Approximately one-third of pediatric epilepsy patients fail to achieve sustained seizure freedom despite receiving two appropriate and well-tolerated antiepileptic drugs. Long-term, recurrent seizures or status epilepticus can severely impact a child' s cognition, memory, quality of life, psychosocial development, and physical growth. Additionally, DRE causes multifaceted irreversible damage to a child' s neurological development. **Objective**: To explore risk factors contributing to DRE in children and its impact on the development of different functional domains in pediatric patients. **Methods**: This study enrolled 250 newly diagnosed pediatric epilepsy patients from the Department of Pediatric Neurology at the Third Affiliated Hospital of Zhengzhou University between January 2023 and October 2024. Based on drug treatment efficacy, they were categorized into a drug-resistant group (n=94) and

a non-drug-resistant group (n=156). A control group of 80 typically developing children who underwent the Chinese version of the Griffiths Mental Development Scale (GDS-C) assessment at the same hospital during the same period served as the normal control group. We collected clinical data and GDS-C assessment results for pediatric patients, evaluating six domains: motor, personal and social, language, eye-hand coordination, performance, and practical reasoning. Statistical analysis was performed using SPSS 25.0 software. Multivariate Logistic stepwise regression analysis was employed to explore risk factors for DRE in children. ROC curve analysis was conducted to evaluate the predictive value of high-risk factors and combined indicators for childhood DRE. **Results**: The drug-resistant group and non-drug-resistant group differed significantly in body weight, age at onset, initial trigger for first seizure, seizure pattern changes, genetic etiology, structural etiology, unknown etiology, pre-treatment seizure duration, pre-treatment seizure frequency, status epilepticus, efficacy of first antiepileptic drug, developmental delay, history of febrile seizures, birth history, fibrinogen, blood ammonia, ceruloplasmin, vitamin D, cranial MRI, initial EEG, EEG after 6 months of treatment, multifocal epileptiform discharges, chromosomal and genetic testing ($P<0.05$). Results of the multivariate Logistic stepwise regression analysis revealed that poor efficacy of the first antiepileptic drug (OR=18.928, 95%CI=8.392-42.693, $P<0.001$), prolonged seizure duration prior to treatment (OR=1.089, 95%CI=1.006-1.180, P=0.036), developmental delay (OR=3.415, 95%CI=1.504-7.754, P=0.003), and multifocal epileptiform discharges (OR=5.265, 95%CI=2.335-11.873, $P<0.001$) were identified as high-risk factors for DRE in children. ROC curve analysis revealed that the combined indicators achieved an area under the curve (AUC) of 0.920 (95%CI=0.887-0.953) for predicting childhood DRE, with an optimal cutoff value of 0.316, sensitivity of 0.904, and specificity of 0.801. Comparisons of developmental quotients across six functional domains among children in the control group, drug-resistant group, and non-drug-resistant group revealed statistically significant differences ($P<0.05$). Specifically, children in the non-drug-resistant group demonstrated higher developmental quotients in motor skills, personal and social skills, language, hand-eye coordination, and performance domains than those in the drug-resistant group, but lower than those in the control group ($P<0.05$). **Conclusion**: Poor response to initial antiepileptic drugs, prolonged seizure duration prior to treatment, developmental delay, and multifocal epileptiform discharges are high-risk factors for childhood DRE. The constructed combined indicator prediction model holds clinical reference value; children with DRE exhibit significant developmental lag across multiple functional domains.

Keywords: Epilepsy; Drug-resistant epilepsy; Child; High-risk factors; Griffiths mental development assessment scale (Chinese version); Functional domain; Developmental quotient

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Epilepsy is a chronic brain disease caused by repeated abnormal neuronal discharges, with a prevalence of 4‰ to 7‰ [1]. Currently, medication remains an

important treatment modality for pediatric epilepsy patients; however, approximately one-third of children fail to achieve complete seizure control despite receiving proper anti-seizure medications (ASMs). Long-term, recurrent seizures or status epilepticus can severely impact a child' s cognition, memory, quality of life, psychosocial development, and physical growth. Furthermore, numerous studies indicate that children with drug-resistant epilepsy (DRE) have a mortality rate three times higher than that of the general population [2]. This study aims to analyze high-risk factors for childhood DRE and develop an ROC curve to identify the optimal predictive model, providing a theoretical basis for early clinical identification of pediatric DRE. Additionally, through the Griffiths Developmental Scales-Chinese version (GDS-C), we investigate the impact of DRE on development across different functional domains to provide evidence for early targeted rehabilitation interventions for children with DRE.

1.1 Study Subjects

We selected 250 newly diagnosed pediatric epilepsy patients from the Department of Pediatric Neurology at the Third Affiliated Hospital of Zhengzhou University between January 2023 and October 2024 as our study subjects. Based on treatment response, they were divided into a drug-resistant group (n=94) and a non-drug-resistant group (n=156). Additionally, 80 typically developing children who underwent GDS-C assessment at the same hospital during the same period were selected as the normal control group. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University (2024-422-01), and informed consent was obtained from all participating children and their families.

1.1.1 Inclusion Criteria

1. Age 0-8 years;
2. All patients met the diagnostic criteria for epilepsy and/or DRE established by the International League Against Epilepsy (ILAE) in 2017, where DRE is defined as failure to achieve sustained seizure freedom despite adequate trials of two tolerated antiepileptic drugs (monotherapy or combination therapy) [3];
3. Complete medical records with readily available clinical examination and test results.

1.1.2 Exclusion Criteria

1. Presence of severe systemic diseases, such as congenital heart disease or severe hepatic/renal disorders;
2. Poor compliance of guardians or children, preventing completion of standardized systematic treatment;
3. Lack of GDS-C assessment data.

1.2 Methods

1.2.1 General Data Collection This retrospective case-control study collected general patient data through the hospital' s electronic medical record system, including: name, sex, age, body weight, age at onset, time from onset to antiepileptic drug initiation, etiology, seizure pattern changes, status epilepticus, symptomatic epilepsy syndromes, efficacy of first antiepileptic drug, intellectual disability, comorbidities, history of febrile seizures, history of brain infection, abnormal birth history, and family history.

1.2.2 Laboratory Examination Indicators Laboratory tests included: fibrinogen, blood ammonia, ceruloplasmin, vitamin D, parathyroid hormone, lactate, homocysteine, genetic metabolic disease screening, cranial MRI, initial EEG, EEG after 6 months of treatment, and chromosomal and genetic testing.

1.2.3 Developmental Assessment The GDS-C, revised and developed based on the Griffiths Developmental Scales-II Enhanced Edition, features Chinese norms and complete intellectual property rights, and is considered the "gold standard" for child developmental assessment [4]. Applicable to children aged 0-8 years, the GDS-C primarily evaluates neuropsychomotor developmental delay across six domains: motor, personal and social, language, hand-eye coordination, performance, and practical reasoning. The Third Affiliated Hospital of Zhengzhou University is one of the institutions that established the GDS-C norms and has extensive clinical application experience.

GDS-C assessments were conducted in dedicated rooms by qualified, experienced professionals. The assessment yielded developmental age-equivalent scores for each domain, from which developmental quotients (DQ) were calculated (DQ = developmental age-equivalent / chronological age $\times$ 100). Assessment standards: DQ $\geq$ 85 indicated normal development, DQ 70-84 indicated borderline status, and DQ $<$ 70 indicated developmental delay.

1.3 Statistical Analysis Data analysis was performed using SPSS 25.0 software. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and compared between two groups using independent samples t-tests; comparisons among multiple groups used one-way ANOVA with pairwise comparisons conducted using LSD-t tests. Non-normally distributed continuous variables were expressed as M(P25, P75) and compared using Mann-Whitney U tests. Categorical variables were expressed as frequencies and compared using χ^2 tests. Variables with statistical significance in univariate analysis were entered into multivariate Logistic stepwise regression analysis to explore high-risk factors for childhood DRE. ROC curves were plotted for high-risk factors and combined indicators to predict childhood DRE. $P<0.05$ was considered statistically significant.

2.1 Univariate Analysis of High-Risk Factors for Childhood DRE

Univariate analysis revealed no significant differences between the drug-resistant and non-drug-resistant groups in sex, time from onset to diagnosis, metabolic etiology, infectious etiology, immune etiology, comorbidities, neonatal seizure history, brain trauma history, brain infection history, paternal family history, or maternal family history ($P>0.05$). However, significant differences were observed between the two groups in body weight, age at onset, initial seizure trigger, seizure pattern changes, genetic etiology, structural etiology, unknown etiology, pre-treatment seizure duration, pre-treatment seizure frequency, status epilepticus, efficacy of first antiepileptic drug, developmental delay, history of febrile seizures, birth history, fibrinogen, blood ammonia, ceruloplasmin, vitamin D, cranial MRI, initial EEG, EEG after 6 months of treatment, multifocal epileptiform discharges, and chromosomal and genetic testing ($P<0.05$). See Table 1 and Table 2 .

2.2 Multivariate Logistic Stepwise Regression Analysis of High-Risk Factors for Childhood DRE

Variables showing statistical significance in univariate analysis, excluding collinear factors and considering clinical relevance, were entered as independent variables into multivariate Logistic stepwise regression analysis with childhood DRE diagnosis as the dependent variable (variable assignments shown in Table 3). Results revealed that poor efficacy of the first antiepileptic drug (OR=18.928, 95%CI=8.392-42.693, $P<0.001$), prolonged pre-treatment seizure duration (OR=1.089, 95%CI=1.006-1.180, $P=0.036$), developmental delay (OR=3.415, 95%CI=1.504-7.754, $P=0.003$), and multifocal epileptiform discharges (OR=5.265, 95%CI=2.335-11.873, $P<0.001$) were independent high-risk factors for childhood DRE. See Table 4 .

2.3 ROC Curve Analysis of High-Risk Factors and Combined Indicators for Predicting Childhood DRE

ROC curve analysis demonstrated that the combined indicators achieved an area under the curve (AUC) of 0.920 (95%CI=0.887-0.953) for predicting childhood DRE, with an optimal cutoff value of 0.316, sensitivity of 0.904, and specificity of 0.801. See Table 5 and Figure 1 [Figure 1: see original paper].

2.4 Comparison of Developmental Quotients Across Different Functional Domains Among Three Groups

Comparisons of developmental quotients across six functional domains among children in the control, drug-resistant, and non-drug-resistant groups revealed statistically significant differences ($P<0.05$). Specifically, children in the non-drug-resistant group demonstrated higher developmental quotients in motor, personal and social, language, hand-eye coordination, and performance domains than those in the drug-resistant group, but lower than those in the control group

(P<0.05). There was no significant difference in practical reasoning domain DQ between the drug-resistant and non-drug-resistant groups (P>0.05). See Table 6 .

Discussion

Epilepsy is a common condition in pediatric neurology, with most cases achieving seizure control through standardized treatment; however, approximately 30% of children develop DRE [5]. Frequent seizures cause multifaceted impairments in neurodevelopment, cognition, memory, and psychosocial functioning, leading to intellectual disability and significantly lower quality of life compared to healthy children. Therefore, early identification of high-risk factors for DRE is particularly important [6].

This study found that the efficacy of the first antiepileptic drug is an independent high-risk factor for childhood DRE, consistent with international reports that response to the first antiepileptic drug is a strong predictor of long-term prognosis in pediatric epilepsy patients [7]. Research indicates that children experiencing weekly seizures during the first year of antiepileptic treatment have an eight-fold increased probability of developing DRE, with diminishing treatment efficacy following each medication change. Conversely, children achieving at least one year of seizure freedom have a low probability of developing DRE. This suggests that after initial antiepileptic drug failure, adding other antiepileptic drugs substantially reduces control rates, thereby increasing DRE probability [8]. Poor response to the first antiepileptic drug may indicate underlying structural brain lesions or genetic mutations associated with epilepsy, which inherently predispose to DRE development, resulting in poor seizure control even after adding second or third antiepileptic drugs.

Current domestic and international research consistently demonstrates that children with status epilepticus are more likely to develop DRE, indicating that seizure duration is closely associated with childhood DRE occurrence, which aligns with our finding that prolonged pre-treatment seizure duration is a high-risk factor. At the cellular level, prolonged seizure duration promotes decreased inhibitory neural pathway function, allowing activation of excitatory feedback loops that lead to repetitive, synchronized neuronal discharges [9]. Extended seizures cause gamma-aminobutyric acid (GABA) dysfunction, sustained excitatory input, and neuronal damage or even death, further predisposing to DRE. Moreover, prolonged seizure duration increases complication rates, including cerebral edema and hypoxia, with animal models demonstrating that extended seizures can cause acute hippocampal injury and irreversible brain damage, increasing DRE incidence [10-11].

Developmental delay reduces the probability of seizure control and increases DRE occurrence. Kalilani et al. [12] conducted a systematic review and meta-analysis of 35 epidemiological studies on DRE in children and adults published between January 1, 1980 and July 3, 2015, including 3,941 DRE cases and 13,000

drug-responsive cases, identifying developmental delay as an independent risk factor. Additional studies have also shown that developmental delay increases DRE risk [13], consistent with our findings. Children with developmental delay often have congenital brain structural abnormalities or genetic metabolic disorders and may have epileptic encephalopathy, all of which increase DRE incidence [14].

Multifocal epileptiform discharges represent an independent risk factor for childhood DRE. A foreign study analyzing 229 pediatric epilepsy patients identified multifocal epileptiform discharges as a strong predictor of childhood DRE [15], corresponding with our conclusion. The underlying mechanism involves multiple epileptogenic foci that interact and propagate discharges, resulting in more complex and diverse seizure patterns and increasing seizure control difficulty. Currently, few domestic and international studies have examined similar influencing factors, necessitating larger sample sizes for further validation.

In medical research, ROC curve prediction models offer significant advantages over other models by intuitively displaying data without interference from data category distribution and objectively evaluating overall model performance in distinguishing positive and negative samples [16]. This study employed this model to develop an optimal predictive ROC curve for childhood DRE risk factors, achieving an AUC >0.9 with good model fit, providing clinical reference for identifying children with DRE.

The impact of recurrent seizures on children' s growth and development has garnered widespread medical attention, though differences in effects across functional domains remain unclear. This study evaluated children' s development across different functional domains using GDS-C, finding that children with DRE exhibited lower DQs across all six domains compared to normal children, particularly in hand-eye coordination, consistent with literature reports [17]. The mechanism involves epilepsy-related encephalopathy commonly present in DRE patients, while hand-eye coordination is a dynamic process involving the cerebellum, parietal lobe, frontal lobe, occipital lobe, and basal ganglia, with injury to any region potentially affecting precision. Research indicates that >70% of children with Lennox-Gastaut syndrome have delayed hand-eye coordination development, and early rehabilitation intervention can block epilepsy-related brain damage and reverse developmental stagnation, providing clinical evidence for hand-eye coordination domain recovery [18]. DRE had the smallest impact on practical reasoning domain development, likely because the Griffiths scale primarily evaluates practical reasoning in children >2 years old, and during brain development, DRE patients' structural and functional plasticity allows gradual developmental catch-up, reducing the gap [19]. Therefore, epilepsy treatment should not only focus on seizure control but also monitor children' s growth and development to enable early targeted interventions, particularly for hand-eye coordination training, thereby improving health status and quality of life.

In summary, children with poor response to initial antiepileptic drugs, prolonged pre-treatment seizure duration, developmental delay, and multifocal epilepti-

form discharges on EEG are more likely to develop DRE. Comparison across six GDS-C functional domains reveals that children with DRE lag behind non-DRE children in multiple developmental aspects, particularly in hand-eye coordination, providing clinicians with evidence for early identification of pediatric DRE to enable individualized treatment protocols. We recommend that children with developmental delay undergo early rehabilitation training to improve subsequent health outcomes.

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Author Contributions: LIU Yu conceptualized the study, implemented the research protocol, collected and organized data, performed statistical analysis, designed the article, and drafted the manuscript. KONG Lina analyzed study feasibility. DU Kaixian, GUAN Jing, CHEN Hao, LI Lin, LI Xiao, SONG Panpan, and PENG Yanhua conducted specific experiments. DU Kaixian coor-

dinated the study, revised and approved the final manuscript, provided supervision, and took overall responsibility for the article.

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ORCID IDs: - LIU Yu: https://orcid.org/0009-0003-6947-4917 - DU Kaixian: https://orcid.org/0009-0000-4846-1824

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