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PREDICTION OF INDIVIDUALIZED TREATMENT IN CHILDREN WITH DRUG-RESISTANT EPILEPSY BASED ON CLINICAL, GENETIC AND NEUROIMMUNOLOGICAL PREDICTORS USING ARTIFICIAL INTELLIGENCE

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Abstract

Drug-resistant epilepsy (DRE) in children represents one of the most challenging conditions in pediatric neurology, characterized by persistent seizures despite appropriate antiseizure treatment and a high risk of cognitive, neurodevelopmental, and functional impairment. The aim of this study is to identify clinical, genetic, and neuroimmunological predictors of drug-resistant epilepsy in children and to develop an artificial intelligence-based approach for predicting individualized treatment response. The study will include children with epilepsy with assessment of clinical and neurological characteristics, seizure type and frequency, age at seizure onset, neurodevelopmental status, EEG and MRI findings, genetic variants, and neuroimmunological biomarkers. Clinical, genetic, neuroimmunological, and instrumental parameters will be analyzed using statistical and machine-learning methods. The prognostic significance of individual and combined predictors for drug resistance and treatment response will be determined. Based on the obtained results, an artificial intelligence-based predictive model will be developed to support individualized treatment prognosis in children with epilepsy. The proposed approach is expected to facilitate early identification of children at high risk of drug-resistant epilepsy, improve prediction of treatment response, and contribute to the optimization of individualized therapeutic strategies.

Keywords: drug-resistant epilepsy, children, clinical predictors, genetic predictors, neuroimmunology, artificial intelligence, machine learning, individualized treatment

1. Relevance

Drug-resistant epilepsy (DRE) in children is one of the most important and challenging problems in pediatric neurology. Persistent epileptic seizures despite adequate antiseizure treatment may lead to progressive impairment of cognitive, speech, behavioral, and psychomotor development, reduced quality of life, and an increased risk of long-term neurological disability. The early identification of children at high risk of drug resistance is therefore essential for timely modification of treatment strategies and referral to specialized epilepsy care.

The development of drug-resistant epilepsy is multifactorial and is influenced by the clinical characteristics of seizures, age at onset, underlying structural and genetic abnormalities, neurodevelopmental status, and response to previous antiseizure medications. In recent years, increasing attention has been given to genetic mechanisms of epilepsy, particularly pathogenic variants in genes associated with neuronal excitability, ion-channel function, synaptic transmission, and epileptic encephalopathies. Identification of clinically relevant genetic predictors may contribute to a better understanding of disease heterogeneity and differences in treatment response among pediatric patients.

Neuroimmunological mechanisms are also considered an important component of epileptogenesis and disease progression. Alterations in cellular and humoral immunity, as well as changes in pro- and anti-inflammatory mediators, may contribute to neuronal hyperexcitability and the persistence of epileptic activity. Therefore, the combined assessment of clinical, genetic, and neuroimmunological markers may provide additional information for early prediction of drug resistance and treatment outcomes.

Electroencephalography (EEG) and magnetic resonance imaging (MRI) remain essential tools for assessing the severity and underlying mechanisms of epilepsy. Epileptiform activity, generalized or focal EEG abnormalities, structural brain lesions, cortical malformations, white matter abnormalities, and hippocampal changes may provide important prognostic information. However, the simultaneous analysis of clinical, genetic, neuroimmunological, EEG, and MRI data generates a complex multidimensional dataset that may be difficult to interpret using conventional approaches alone.

In this context, artificial intelligence and machine-learning technologies offer new opportunities for integrating multiple clinical and biological variables and identifying complex patterns associated with drug resistance and treatment response. Development of an artificial intelligence-based predictive model may facilitate early risk stratification of pediatric patients and provide a more individualized approach to treatment planning. Therefore, investigation of clinical, genetic, and neuroimmunological predictors of drug-resistant epilepsy and their integration using artificial intelligence represents a relevant and promising direction in modern pediatric neurology.

Research Objective. The objective of this study is to develop criteria for early diagnosis of epileptic encephalopathy in early childhood based on a comprehensive analysis of clinical, paraclinical, and immunological characteristics, as well as to identify early predictors of drug-resistant forms in order to prevent early neurological disability.

2. Materials and Methods

The study included data from 145 children aged 0 to 3 years diagnosed with epileptic disorders. This was a prospective clinical study aimed at evaluating the clinical, neurophysiological, neuroimaging, and immunological characteristics of early childhood epileptic encephalopathies and identifying markers for early diagnosis and disease severity. All patients were examined and classified according to the ILAE 2025 operational classification of epileptic seizures and epilepsies. The study population was divided into two groups: the main group, consisting of 75 children with epileptic encephalopathy (EE), and the comparison group, which included 70 children with symptomatic epilepsy without signs of epileptic encephalopathy.

Inclusion criteria: confirmed diagnosis of epileptic encephalopathy or symptomatic epilepsy; age from birth to 3 years; presence of epileptic seizures documented clinically and/or by EEG; availability of complete clinical, EEG, MRI, and immunological data; written informed consent from parents or legal guardians. Exclusion criteria: age over 3 years; congenital genetic syndromes (including Down and Rett syndromes); progressive neurodegenerative or severe metabolic disorders; acute infectious or inflammatory diseases (meningitis, encephalitis, sepsis); severe cardiac, hepatic, or renal insufficiency; immunosuppressive therapy; and incomplete diagnostic data.

To achieve the research objectives, a set of clinical, instrumental, laboratory, and immunological methods was used. Clinical evaluation included neurological examination, detailed medical history, seizure semiology, seizure frequency, and assessment of developmental delay or regression.

Neurophysiological assessment was performed using electroencephalography (EEG), with analysis of epileptic encephalopathy–specific patterns such as hypsarrhythmia, modified hypsarrhythmia, burst-suppression, electrical status epilepticus during sleep (ESES), and diffuse or generalized epileptiform discharges. Neuroimaging was conducted using magnetic resonance imaging (MRI) to identify structural brain abnormalities, including cortical dysplasia, ventricular enlargement, periventricular white matter lesions, hypoxic–ischemic changes, and hippocampal sclerosis. Psychomotor and cognitive development was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), which allowed evaluation of cognitive, language, and motor functions. Immunological assessment included evaluation of cellular and humoral immunity parameters, such as $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$ lymphocyte subpopulations, CD4/CD8 ratio, immunoglobulin G (IgG), circulating immune complexes, and cytokine levels (IL-1β, TNF-α, IL-10). Statistical analysis was performed using standard biomedical statistical methods. Quantitative variables were expressed as mean ± standard deviation. Group comparisons and correlation analyses were conducted to assess associations between immunological parameters, EEG findings, neuroimaging changes, and clinical severity. A p-value < 0.05 was considered statistically significant.

Of the 145 children included, the mean age was 17.1 ± 1.09 months. The main group consisted of children with severe, early-onset epileptic encephalopathies, while the comparison group included patients with symptomatic epilepsy and relatively preserved neurodevelopmental profiles.

3. Study Results

Analysis of the clinical characteristics of early childhood epilepsy demonstrated significant differences between children with epileptic encephalopathy (EE) and those with symptomatic epilepsy, reflecting distinct patterns of disease onset, seizure burden, neurodevelopmental impairment, and immunological involvement.

3.1. Clinical onset and seizure characteristics

In the main group (EE, n = 75), epileptic seizures manifested predominantly within the first year of life, with a mean age of onset of 4.6 ± 1.8 months, whereas in the comparison group (symptomatic epilepsy, n = 70), seizure onset occurred later, at 9.2 ± 2.4 months on average. Early onset was significantly associated with more severe clinical presentation and rapid neurodevelopmental regression.

Children with epileptic encephalopathy demonstrated a markedly higher seizure burden. Daily or very frequent seizures (≥5 per day) were observed in 74.7% of EE patients, compared to 28.6% in the symptomatic epilepsy group ($p < 0.001$). Seizure types in the EE group were predominantly epileptic spasms, tonic and myoclonic seizures, often occurring in clusters, whereas focal and secondary generalized seizures were more common in the comparison group. Clinically defined epileptic encephalopathy syndromes were identified mainly in the main group, including West syndrome (61.3%), Lennox–Gastaut syndrome (18.7%), Ohtahara syndrome, and early forms evolving toward mixed encephalopathic patterns. These syndromes were characterized by early onset, polymorphic seizures, and resistance to standard antiepileptic therapy.

3.2. Neurodevelopmental outcomes

Assessment of psychomotor development using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) revealed profound developmental impairment in children with epileptic encephalopathy. Mean composite scores in the EE group ranged between 66–68 points, indicating moderate to severe developmental delay, whereas children with symptomatic epilepsy demonstrated significantly higher scores ($p < 0.01$), corresponding mainly to mild or moderate delay. A statistically significant inverse correlation was identified between seizure frequency and Bayley-III developmental indices ($r = –0.47$), indicating that increasing seizure burden was associated with deeper psychomotor and cognitive impairment. Developmental regression, rather than delay alone, was observed predominantly in the EE group and was closely related to early seizure onset and diffuse EEG abnormalities.

3.3. Electroencephalographic findings

Electroencephalographic analysis revealed marked differences between the study groups. In the EE group, EEG patterns were predominantly diffuse and generalized, reflecting severe functional brain involvement. Modified hypsarrhythmia was detected in 37.3% of EE patients compared to only 1.43% in the symptomatic epilepsy group ($p < 0.00000001$), confirming its strong association with epileptic encephalopathy. Other encephalopathy-specific EEG patterns, including burst-suppression and electrical status epilepticus during sleep (ESES), were observed exclusively in the EE group, indicating severe early epileptic network dysfunction. In contrast, focal epileptiform discharges were significantly more common in the symptomatic epilepsy group ($p < 0.00001$), consistent with localized structural or acquired brain lesions. Correlation analysis demonstrated a moderate positive relationship between the severity of EEG abnormalities and clinical disease severity ($r = 0.55$; $R^2 = 0.30$), underscoring the prognostic value of diffuse EEG disturbances in epileptic encephalopathy.

3.4. Neuroimaging results

Magnetic resonance imaging (MRI) findings further supported the distinction between the two groups. Children with epileptic encephalopathy exhibited a significantly higher prevalence of severe structural brain abnormalities. Ventriculomegaly was detected in 48% of EE patients ($p < 0.00001$), with grade III ventricular dilation observed exclusively in this group. Cortical atrophy was significantly more frequent in the EE group (49.3%; $p < 0.001$), and diffuse cortical atrophy was identified only among children with epileptic encephalopathy. Additionally, subcortical structure atrophy and periventricular white matter lesions were more prevalent in the EE group ($p < 0.001$). A particularly important finding was the significantly higher incidence of cortical dysplasia in epileptic encephalopathy (44% vs. 8.57%; $p < 0.0000015$), especially multifocal forms, indicating the major role of congenital brain malformations in early epileptogenesis. The increased frequency of hippocampal sclerosis and post-hypoxic changes further emphasized the association between severe early epileptic encephalopathy and perinatal hypoxic–ischemic injury.

3.5. Immunological findings

Immunological analysis revealed pronounced immune dysregulation in children with epileptic encephalopathy. In the EE group, a trend toward reduced B-lymphocyte ($CD72^+$) levels was observed,

though without statistical significance ($p > 0.05$). In contrast, a significant decrease in IgA levels ($p = 0.0001$) indicated impaired humoral immune protection. Conversely, IgG levels and circulating immune complexes (CIC) were significantly elevated ($p \leq 0.001$), suggesting chronic immune activation and the involvement of autoimmune mechanisms. Cytokine profiling demonstrated a marked predominance of proinflammatory mediators. IL-1β levels were significantly increased in the EE group ($p = 0.0001$), reflecting active neuroinflammation and its contribution to epileptic activity. TNF-α showed an increasing trend, approaching statistical significance ($p = 0.051$), while IL-10, an anti-inflammatory cytokine, was reduced, indicating insufficient immunoregulatory control.

3.6. Correlation between immunological markers and clinical severity

A moderate positive correlation was identified between immunological markers and clinical severity indices in children with epileptic encephalopathy ($r = 0.42$; $p < 0.05$). Increasing disease severity was associated with higher levels of proinflammatory cytokines (IL-1β, TNF-α), elevated IgG and CIC, and a reduction in IL-10 and the CD4/CD8 ratio. These findings indicate that immune imbalance is closely linked to severe clinical phenotypes and supports the role of immunological markers as additional biomarkers for early diagnosis, disease stratification, and prognosis in epileptic encephalopathy.

4. Conclusions

The present study demonstrates that early childhood epileptic encephalopathies are severe neurological conditions characterized not only by early-onset, frequent, and drug-resistant seizures, but also by profound neurodevelopmental impairment and pronounced immune dysregulation. The obtained results confirm that epileptic encephalopathy differs fundamentally from symptomatic epilepsy in terms of clinical severity, electroencephalographic patterns, neuroimaging findings, and immunological profiles. Children with epileptic encephalopathy exhibited significantly earlier seizure onset, higher seizure frequency, and more severe psychomotor regression compared to patients with symptomatic epilepsy. Diffuse and generalized EEG abnormalities, including modified hypsarrhythmia, burst-suppression, and ESES, were closely associated with disease severity and developmental outcomes, highlighting their key diagnostic and prognostic value. A major finding of this study is the identification of marked immunological imbalance in epileptic encephalopathy. Predominance of proinflammatory mechanisms, reflected by elevated IL-1β, increased circulating immune complexes, and higher IgG levels, combined with reduced anti-inflammatory regulation (IL-10, CD4/CD8 ratio), indicates active neuroinflammatory involvement in epileptogenesis. The established correlations between immunological markers, EEG severity, and clinical manifestations support the pathogenetic role of immune-mediated mechanisms in the progression of epileptic encephalopathy. The integration of immunological assessment with clinical, EEG, MRI, and developmental evaluations significantly enhances early diagnosis and risk stratification in children with epileptic encephalopathy. This comprehensive approach allows for improved prognostic assessment and provides a scientific basis for individualized therapeutic strategies, including consideration of immunomodulatory interventions.

In conclusion, the study confirms that immunological markers represent valuable additional biomarkers in early childhood epileptic encephalopathy. Their use, alongside standard clinical and instrumental methods, may contribute to earlier diagnosis, more accurate prognosis, prevention of

severe neurodevelopmental disability, and improvement of long-term outcomes in this vulnerable patient population.

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