BMC Pediatrics

RESEARCH Open Access

Immunological factors in pediatric generalized and focal epilepsy: interplay with anti-seizure medications

Dongyan Zhang[1*] and Hongan Sun[2]

Abstract

Background Pediatric epilepsy presents challenges in treatment optimization, with a significant proportion of patients experiencing inadequate seizure control despite anti-seizure medications (ASMs) therapy. Recent research has indicated the involvement of neuroinflammation and immune-mediated mechanisms in epilepsy pathogenesis, suggesting a potential interplay between immunological factors and ASMs responsiveness. This study aimed to investigate the role of immunological factors in pediatric generalized, focal epilepsy and their interaction with ASMs mechanisms to understand their potential influence on treatment outcomes.

Methods A retrospective cohort study was conducted involving 136 pediatric epilepsy patients, categorized into Anti-seizure medications Insensitive Group ($n=67$) and Anti-seizure medications Sensitive Group ($n=69$). Immunoglobulin levels and immunological factors, including cytokines, were assessed before treatment. Seizure characteristics and ASMs levels were also analyzed. Associations between immunological factors, seizure characteristics, and ASMs sensitivity was evaluated.

Results The study revealed significant differences in immunological factors, including interleukin-6 (IL-6), IL-1β and IL-10 levels, between the insensitive and sensitive groups. Furthermore, seizure frequency, drug-resistant seizures, seizure severity, seizure-free period, and status epilepticus all demonstrated significant correlations with the sensitivity to ASMs, with negative correlations for seizure frequency, drug-resistant seizures, seizure severity, and positive correlations for seizure-free period and status epilepticus.

Conclusion The study highlights the complex interplay between immune function, seizure characteristics, and ASMs mechanisms, underscoring the need for a comprehensive understanding of the immunological modulation of drug response in pediatric epilepsy.

Clinical trial number Not applicable.

Keywords Immunological factors, Pediatric, Epilepsy, Anti-seizure medications

*Correspondence:
Dongyan Zhang
zhangdongyan2024@163.com
[1]Department of Pediatrics II, Maternity & Child Care Center of Qinhuangdao, No. 452 Hongqi North Road, Haigang District, Qinhuangdao City, Hebei Province 066000, P. R. China
[2]Department of Rehabilitation, Qinhuangdao Jianyi Hospital, Qinhuangdao, China

Introduction

Epilepsy is a chronic neurological disorder characterized by an enduring predisposition to generate epileptic seizures, affecting approximately 50 million people worldwide, with a higher prevalence in pediatric populations [1, 2]. Pediatric epilepsy encompasses diverse seizure types, including generalized and focal epilepsy, each associated with distinct pathophysiological mechanisms and treatment responses. While anti-seizure medications (ASMs) constitute the cornerstone of epilepsy management, a substantial proportion of pediatric patients continue to experience inadequate seizure control, highlighting the complex and multifactorial nature of drug responsiveness in this population [3–5]. Recent research has demonstrated the presence of neuroinflammation in epilepsy, characterized by the activation of glial cells, release of pro-inflammatory cytokines, and disruption of the blood-brain barrier, creating a neurotoxic environment conducive to seizure generation and propagation [6, 7]. Moreover, immune-mediated mechanisms have been shown to interact with ASMs pharmacokinetics and pharmacodynamics, suggesting the potential for immunological factors to modulate drug response and treatment outcomes in pediatric epilepsy [8, 9].

In recent years, research efforts have increasingly focused on unraveling the intricate interplay between the immune system and epileptogenesis, shedding light on the potential impact of immune dysregulation on ASMs responsiveness. The traditional view of epilepsy as a purely neuronal disorder has evolved to encompass the bidirectional communication between the nervous and immune systems, with growing recognition of the immunomodulatory effects on neuronal excitability and seizure susceptibility [10]. Pediatric epilepsy, in particular, presents unique challenges in treatment optimization, necessitating a comprehensive understanding of the complex mechanisms underlying drug responsiveness to improve therapeutic outcomes and quality of life for affected children [11]. This study aimed to investigate the role of immunological factors in pediatric epilepsy and their interplay with ASMs mechanisms, with a specific focus on understanding the potential influence of immune dysregulation on treatment outcomes. By examining immunoglobulin levels, immunological factors, and seizure characteristics in relation to ASMs sensitivity, this study sought to elucidate the complex interactions between the immune system, neuronal excitability, and drug responsiveness in pediatric epilepsy.

Methods

Study design and population

This study was a retrospective cohort study that included 136 pediatric epilepsy patients admitted to our hospital between January 2023 and December 2023, who met the inclusion and exclusion criteria. These 136 patients were categorized into two groups based on their response to ASMs. Anti-seizure Medications Insensitive Group ($n=67$): Patients in this group had experienced insufficient seizure control despite adequate doses of ASMs. Anti-seizure Medications Sensitive Group ($n=69$): Patients in this group demonstrated adequate seizure control with the current ASMs therapy. Seizure control was defined as having a $\geq 50\%$ reduction in seizure frequency, or being seizure-free for at least 6 months on the current ASMs regimen. Pediatric patients were stratified based on seizure type into generalized epilepsy or focal epilepsy, as per the International League Against Epilepsy (ILAE) 2017 classification system [12]. In this study, eligible patients had confirmed diagnoses of generalized epilepsy (e.g., absence seizures, generalized tonic clinic seizures) or focal epilepsy (e.g., focal aware seizures, focal impaired-awareness seizures). The inclusion criteria encompassed individuals aged between 3 and 14 years, demonstrating an abrupt onset of rhythmic EEG activity lasting at least 10 s, with concomitant changes in a minimum of 2 of the following characteristics: amplitude, frequency, or spatial distribution. On the other hand, the exclusion criteria entailed the prohibition of patients with prior anti-seizure usage, except for short-acting benzodiazepines administered for sedation over 24 h before enrollment, as well as individuals with serum creatinine levels surpassing 1.6 mg/dL, or seizures arising from correctable metabolic irregularities such as hypoglycemia or hypocalcemia. Patients with unclassified seizure types or overlapping syndromes were excluded to reduce heterogeneity. Additionally, individuals in a terminal medical condition and those in whom EEG monitoring could not be initiated before the urgent treatment of clinical seizures were also omitted from the study. This study was approved by the Ethics Committee of Maternity & Child Care Center of Qinhuangdao in accordance with regulatory and ethical guidelines pertaining to retrospective research studies (Approval number: 2024-03-064). The procedures were conducted in accordance with the ethical standards set forth by the Committee on Human Experimentation and the Helsinki Declaration of 1964, as revised in 2013. Given that this retrospective study utilized de-identified patient data, there was no potential for harm or impact on patient care. Therefore, informed consent was waived. This waiver was approved by the institutional review board and ethics committee of our institution in accordance with regulatory and ethical guidelines pertaining to retrospective studies.

Data collection

Patient demographic information, including age, gender, duration of epilepsy, family history, parental education level, maternal age at birth, paternal age at birth, maternal

smoking during pregnancy, birth weight, family history of epilepsy, family history of autoimmune diseases, family history of allergies was collected and recorded from the medical records system.

Anti-seizure medications levels

After the initiation of anti-seizure medication treatment, 5 ml of fasting venous blood was collected. This collection occurred at a standardized time point following the administration of the primary anti-seizure medication (Valproic Acid, Carbamazepine, Levetiracetam, Phenobarbital, or Phenytoin), as part of the routine clinical monitoring of drug levels. Blood samples were collected regardless of other anti-epileptic therapies already in use. The exact timing of blood collection was not randomized due to the retrospective design of the study. For this reason, the timing of blood collection may vary based on the patient's routine treatment schedule. Homogeneous enzyme immunoassay was used to detect the blood drug concentrations of Valproic Acid (using the valproic acid test kit from Roche Diagnostics) and Carbamazepine (using the carbamazepine test kit from Randox Laboratories). Additionally, 5 ml of plasma was obtained and chromatography was used to measure the blood drug concentrations of Levetiracetam, Phenobarbital, and Phenytoin (using the GI3000-YT blood drug concentration analyzer from Etachem Scientific Instruments).

Immunological factors

Immunoglobulin levels were assessed as follows, 5 ml of fasting venous blood was collected in the morning between 7:00 and 9:00 AM to account for potential diurnal variations in cytokine levels. Samples were centrifuged at a speed of 3,000 rpm for 5 min to obtain the serum for testing. Enzyme-linked immunosorbent assay was used to measure the immunoglobulin levels, utilizing reagent kits obtained from Shanghai Enzyme-linked Biological Technology Co., Ltd. Moreover, a fasting 5 ml blood sample was obtained from the antecubital vein in the morning for blood testing before treatment. The sample was centrifuged at a speed of 3000 rpm for 5 min, and the resulting supernatant was utilized for the analysis of TNF-α, TGF-β, IFN-gamma, IL-1β, IL-6, and IL-10. Enzyme-linked immunosorbent assay was employed for the testing, using reagent kits obtained from Shanghai Enzyme-linked Biological Technology Co., Ltd.

Seizure frequency and severity

Following treatment, the patients' seizure occurrence and severity were recorded, including the monthly frequency of seizures, drug-resistant seizures percentage, seizure severity, seizure-free period (months), and status epilepticus percentage. A seizure severity score was utilized to assess the severity of the seizures, with a range of 0–10 points, where a higher score indicated more severe symptoms.

Statistical analysis

The data analysis was conducted using SPSS 29.0 statistical software (SPSS Inc, Chicago, IL, USA). Categorical data was presented in the form of [n (%)]. For the chi-square test, sample sizes of ≥ 40 were considered, and the chi-square test was applied when the theoretical frequency (T) in each cell of the contingency table was ≥ 5. If the sample size was ≥ 40 but the theoretical frequency (T) was between 1 and 5 ($1 \leq T < 5$), the chi-square test with Yates' continuity correction was used. For sample sizes < 40 or when the theoretical frequency (T) was < 1, the Fisher exact test was employed to account for small sample sizes or low expected frequencies in the contingency table. The Shapiro-Wilk test was utilized to assess the normal distribution of continuous variables. For normally distributed continuous variables, they were presented in the form of mean ± standard deviation (SD) and analyzed using the t-test with corrected variance. Non-normally distributed data was represented in the form of median (25th percentile, 75th percentile) and analyzed using the Wilcoxon rank-sum test. A two-tailed $P < 0.05$ was considered statistically significant. The relationship between continuous variables (IL-6 Level, IL-1β, IL-10 Level, Seizure frequency, Seizure severity, Seizure-free period) and antiepileptic drug sensitivity was assessed using Pearson correlation analysis, while the relationship between categorical variables (Status Epilepticus, Drug-resistant seizures) and antiepileptic drug sensitivity was evaluated using Spearman correlation analysis.

Results

Demographic characteristics

There were no statistically significant differences between the two groups in terms of age, gender distribution, duration of epilepsy, family history of epilepsy, parental education level, maternal and paternal age at birth, maternal smoking during pregnancy, birth weight, family history of autoimmune diseases, allergies, and neurodevelopmental disorders ($P > 0.05$). These findings suggest that the demographic factors analyzed did not have a significant impact on the sensitivity to anti-seizure medications among pediatric patients with epilepsy (Table 1).

Anti-seizure medications levels

There were no statistically significant differences between the two groups in the levels of valproic acid, carbamazepine, levetiracetam, phenobarbital, and phenytoin ($P > 0.05$) (Fig. 1). These results indicate that the levels of anti-seizure medications after treatment did not show significant variations between the insensitive and sensitive groups. However, it is important to note that

Table 1 Demographic characteristics of Anti-seizure medications insensitive and sensitive groups

Demographic characteristic	Anti-seizure medications insensitive group ($n=67$)	Anti-seizure medications sensitive group ($n=69$)	t/χ^2	*P*
Age (years)	7.84 ± 2.15	7.45 ± 2.10	1.077	0.284
Gender				
Male	38 (56.72%)	41 (59.42%)	0.021	0.884
Female	29 (43.28%)	28 (40.58%)		
Family History				
Yes	14 (20.9%)	15 (21.74%)	0.000	1.000
No	53 (79.1%)	54 (78.26%)		
Duration of Epilepsy (years)	4.57 ± 1.9	4.35 ± 1.8	0.701	0.485
Parental Education Level (years)	13.6 ± 2.50	13.8 ± 2.30	0.477	0.634
Maternal Age at Birth (years)	30.5 ± 4.10	30.2 ± 3.80	0.447	0.656
Paternal Age at Birth (years)	32.1 ± 4.50	31.8 ± 4.30	0.403	0.688
Maternal Smoking during Pregnancy				
Yes	28 (41.79%)	26 (37.68%)	0.099	0.753
No	39 (58.21%)	43 (62.32%)		
Birth Weight (g)	3200 ± 400	3150 ± 380	0.747	0.456
Family History of Epilepsy	24 (35.82%)	22 (31.88%)	0.092	0.761
Family History of Autoimmune Diseases	11 (16.42%)	12 (17.39%)	0.000	1.000
Family History of Allergies	18 (26.87%)	20 (28.99%)	0.007	0.933
Family History of Neurodevelopmental Disorders	9 (13.43%)	11 (15.94%)	0.029	0.864

variations in body composition, such as body fat percentage, muscle mass, and hydration status, which were not explicitly controlled for in this study, may influence the pharmacokinetics and pharmacodynamics of these medications.

Analysis of immunological factors

There was no statistically significant difference in the pre-treatment immunoglobulin levels of IgG, IgM, IgA, IgE and IgD between the two groups (Fig. 2). In addition, there were statistically significant differences in the levels of IL-6, IL-1β and IL-10 between the two groups, while there were no statistically significant differences in the levels of TNF-α, TGF-β, and IFN-gamma (Fig. 3).

Seizure frequency and severity

There were statistically significant differences between the two groups in seizure frequency, the percentage of drug-resistant seizures, seizure severity, seizure-free period and the incidence of status epilepticus (Table 2).

Correlation analysis

The correlation analysis between various parameters and the sensitivity to ASMs revealed significant findings (Table 3). The levels of IL-6, IL-1β, and IL-10 showed negative correlations with the sensitivity to ASMs. Furthermore, seizure frequency, drug-resistant seizures, seizure severity, seizure-free period, and status epilepticus all demonstrated significant correlations with the sensitivity to ASMs, with negative correlations for seizure frequency, seizure severity, and positive correlations for seizure-free period and status epilepticus.

Discussion

One of the key findings of this study was the differential sensitivity to antiepileptic medications among pediatric patients with epilepsy. While no statistically significant differences were observed in the levels of anti-seizure medications after treatment between the insensitive and sensitive groups, it is essential to recognize the potential influence of physiological factors, such as body composition, on drug sensitivity. Variations in body fat, muscle mass, and hydration status can affect the distribution, metabolism, and elimination of anti-seizure medications, potentially contributing to differences in therapeutic responses. Although our study did not adjust for these variables, acknowledging their role provides a more nuanced understanding of the factors influencing drug efficacy in pediatric epilepsy. Future research should integrate these parameters to refine assessments of ASMs responsiveness This highlights the multifaceted nature of drug responsiveness in epilepsy, suggesting that factors beyond medication levels play a crucial role in determining treatment outcomes. Notably, the observation that immunological factors, particularly IL-6, IL-1β, and IL-10, displayed significant differences between the insensitive and sensitive groups underscores the potential impact of the immune system on the response to ASMs.

The presence of altered immunological factors in the insensitive group may suggest an association between inflammatory processes and ASMs responsiveness in pediatric epilepsy, though causality cannot be established due to the retrospective nature of this study. Neuroinflammation, characterized by the release of pro-inflammatory cytokines such as IL-6 and IL-1β, both of which are associated with reduced GABAergic inhibition of signaling and enhanced glutamatergic excitatory activity, which may exacerbate neuronal hyperexcitability [13–15]. There has been shown in experimental studies to modulate neuronal excitability, synaptic plasticity, and blood-brain barrier integrity, potentially influencing seizure susceptibility and epileptogenesis [16, 17]. These mechanistic insights provide a basis for further investigations into immune-mediated modulation of ASMs efficacy. While our findings align with these observations,

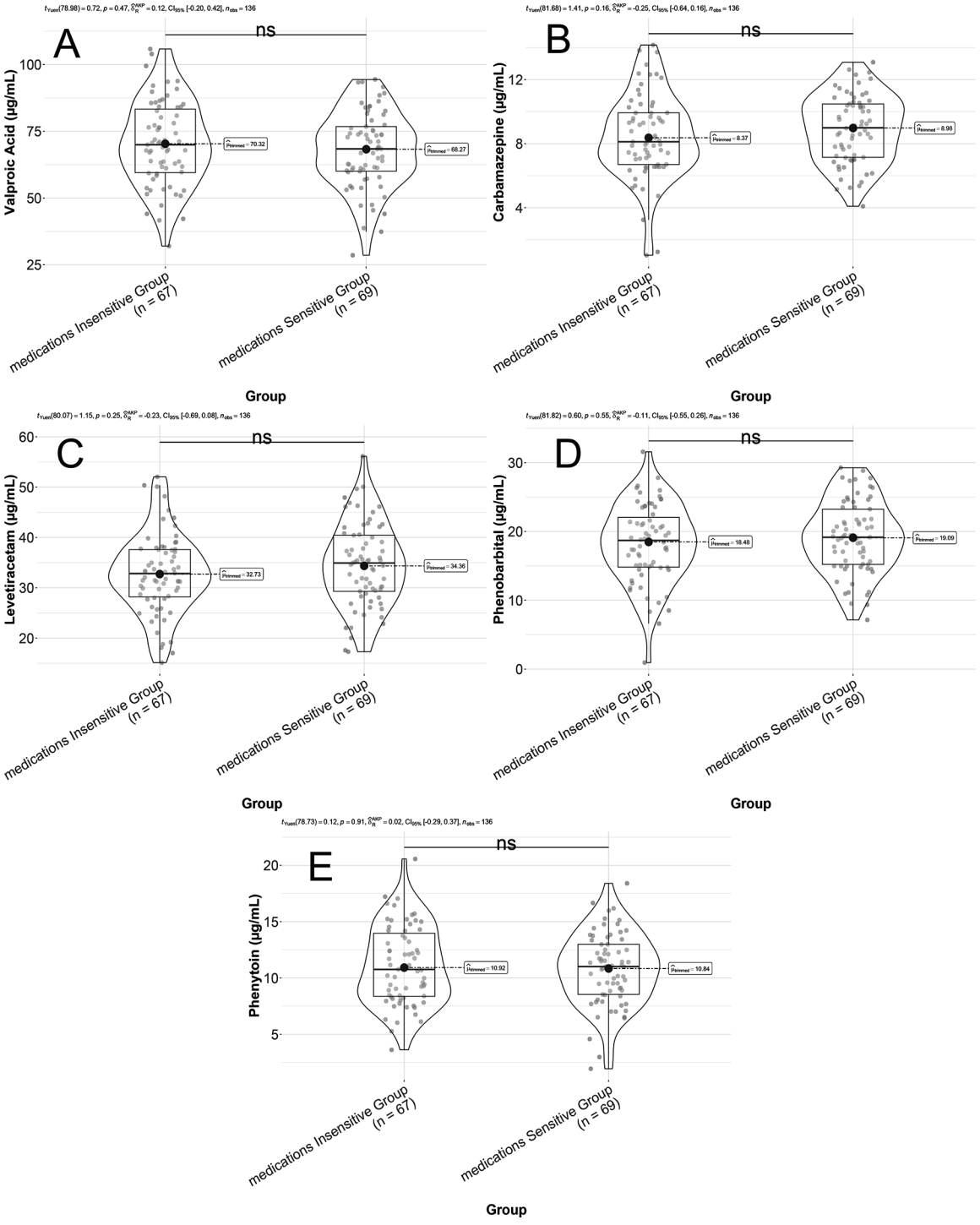

Fig. 1 Anti-seizure medications Levels after treatment. There was no statistically significant difference in the levels of valproic acid, carbamazepine, levetiracetam, phenobarbital and phenytoin sodium in groups Anti-seizure medications Insensitive Group and Anti-seizure medications Sensitive Group. *$P < 0.05$, **$P < 0.01$, *** $P < 0.001$, ns means $P > 0.05$

the retrospective design precludes definitive conclusions about causal relationships. Future prospective studies with experimental validation are necessary to explore these mechanisms in greater detail. In the context of antiepileptic drug sensitivity, the observed negative correlations between IL-6, IL-1β, and IL-10 levels and drug sensitivity suggest a potential link between immunological dysregulation and altered pharmacological responses, highlighting the potential interplay between immune factors and response to ASMs. These findings

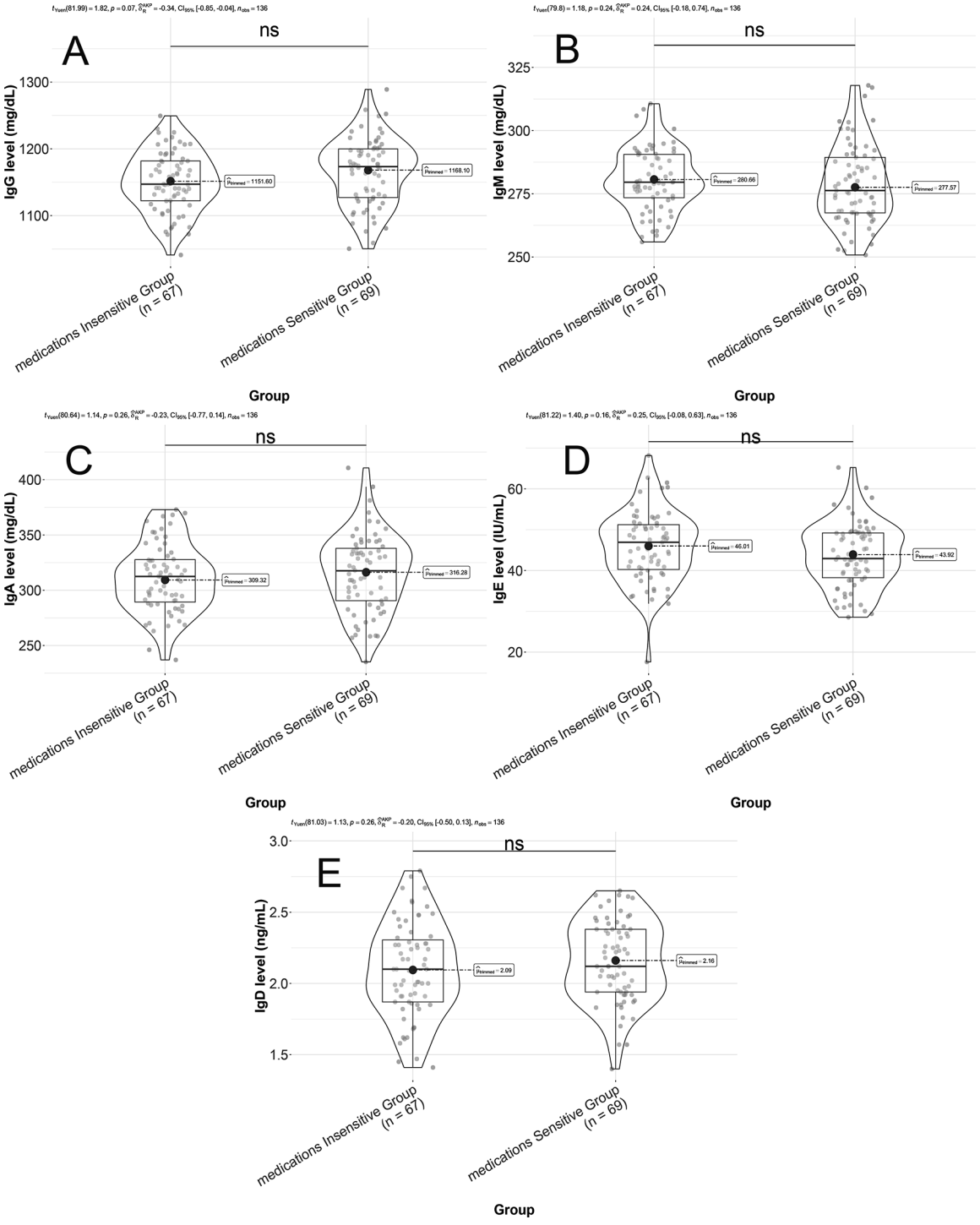

Fig. 2 Comparison of Immunoglobulin Levels before treatment. There was no statistically significant difference in the pretreatment levels of IgG, IgM, IgA, IgE, and IgD immunoglobulins between groups Anti-seizure medications Insensitive Group and Anti-seizure medications Insensitive Group. *$P < 0.05$, **$P < 0.01$, *** $P < 0.001$, ns means $P > 0.05$

align with previous studies implicating immune dysregulation in drug-resistant epilepsy, highlighting the need to explore the immune-mediated mechanisms underlying treatment resistance [18–20]. Furthermore, the significant correlations between seizure frequency, drug-resistant seizures, seizure severity, seizure-free period, and status epilepticus with antiepileptic drug sensitivity underscore the intricate relationship between seizure characteristics and treatment response [21–23]. The negative associations observed between these seizure

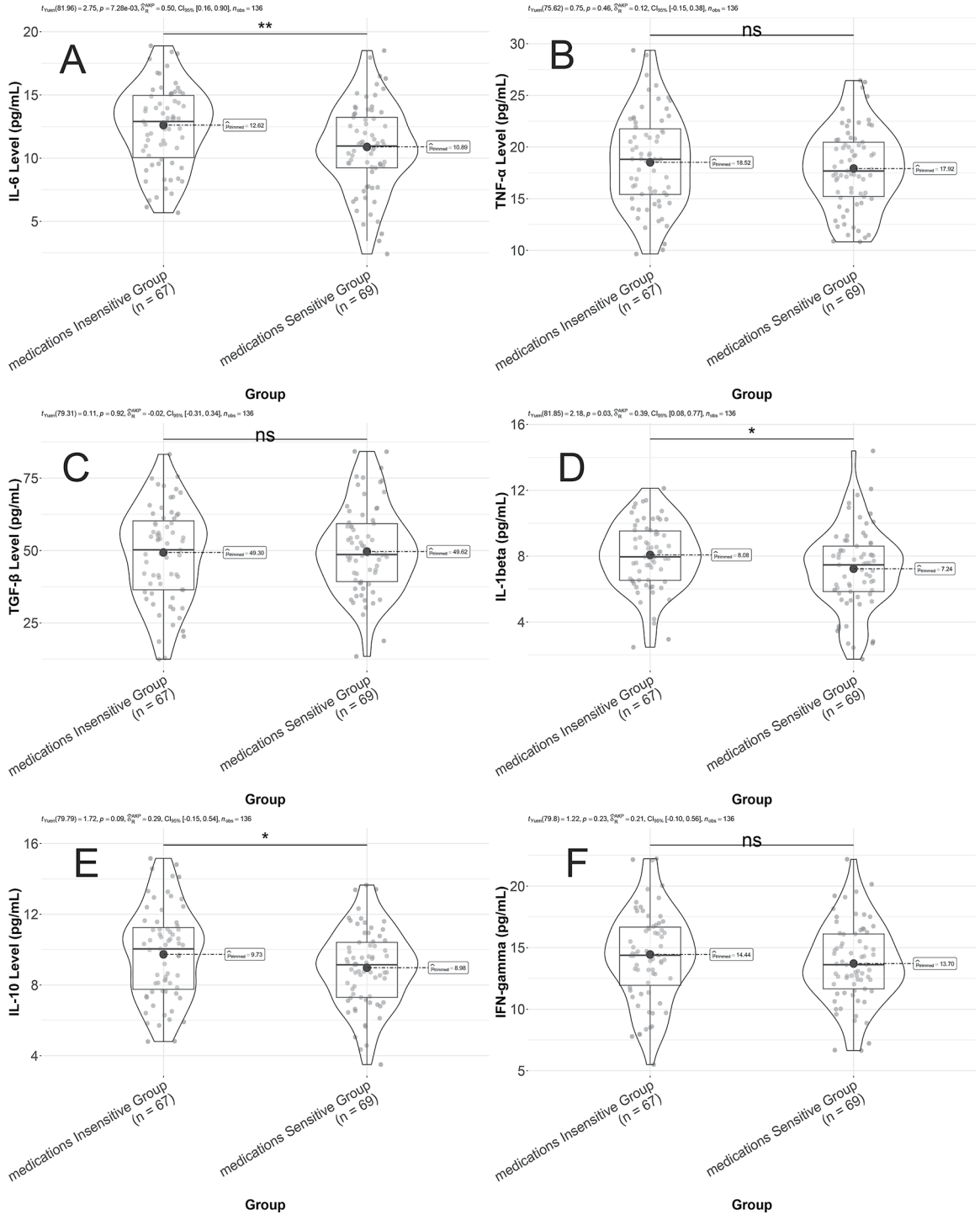

Fig. 3 Immunological Factors before treatment. There was a statistically significant difference in the levels of IL-6, IL-1β, and IL-10 between groups Anti-seizure medications Insensitive Group and Anti-seizure medications Insensitive Group, while there was no statistically significant difference in the levels of TNF-α, TGF-β, and IFN-γ. *$P < 0.05$, **$P < 0.01$, *** $P < 0.001$, ns means $P > 0.05$

parameters and drug sensitivity suggest that patients with higher seizure frequency, drug-resistant seizures, and increased seizure severity was more likely to exhibit reduced sensitivity to antiepileptic medications. These findings emphasize the clinical relevance of considering seizure characteristics in treatment decision-making and highlight the potential utility of immunological markers as adjunctive predictors of drug response.

The intricate crosstalk between the immune system, neuronal excitability, and antiepileptic drug mechanisms

Table 2 Seizure frequency and severity after treatment

Parameter	Anti-seizure medications Insensitive Group ($n=67$)	Anti-seizure medications Sensitive Group ($n=69$)	t	*P*
Seizure frequency (per month)	5.20 ± 1.30	3.80 ± 1.20	6.511	< 0.001
Drug-resistant seizures (%)	40 (59.7%)	24 (34.78%)	7.502	0.006
Seizure severity (1–10 scale)	7.20 ± 1.50	5.40 ± 1.30	7.493	< 0.001
Seizure-free period (months)	12.10 ± 2.50	15.6 ± 3.10	7.271	< 0.001
Status Epilepticus (%)	7 (10.45%)	24 (34.78%)	10.098	0.001

Table 3 Correlation analysis between various parameters and the sensitivity to ASMs

Parameter	*r*	R^2	*P*
IL-6 Level (pg/mL)	-0.247	0.061	0.004
IL-1β (pg/mL)	-0.179	0.032	0.038
IL-10 Level (pg/mL)	-0.175	0.031	0.041
Seizure frequency (per month)	-0.491	0.241	< 0.001
Drug-resistant seizures (%)	-0.250	0.062	0.003
Seizure severity (1–10 scale)	-0.544	0.296	< 0.001
Seizure-free period (months)	0.531	0.282	< 0.001
Status Epilepticus (%)	0.290	0.084	< 0.001

*r: correlation coefficient, which reflects the degree of linear correlation between two variables. R^2: coefficient of determination, which indicates the proportion of a variable that can be explained by another variable

underpins the need to adopt a holistic approach to pediatric epilepsy management. While ASMs primarily target neuronal ion channels and neurotransmitter systems, it was increasingly recognized that the immune system exerts a modulatory influence on these processes [24, 25]. For instance, pro-inflammatory cytokines can alter the expression and function of drug-metabolizing enzymes and transporters, potentially impacting drug pharmacokinetics and pharmacodynamics. This immune-mediated modulation of drug metabolism and transport may contribute to varied drug responses among patients, highlighting the importance of considering immunological factors in individualizing treatment strategies [26, 27]. Moreover, the bidirectional relationship between epilepsy and immune dysfunction underscores the potential for targeted immunomodulatory approaches in epilepsy management. Evidence suggests that immunotherapies, including anti-inflammatory agents and immunomodulators, hold promise in mitigating seizure activity and modifying disease progression in certain epilepsy subtypes [9, 28]. Neuroinflammation can lead to seizures and recurrences by increasing neuronal excitability [29]. By targeting immune dysregulation, these therapies aim to rebalance the pro-inflammatory and anti-inflammatory milieu in the brain, potentially enhancing drug responsiveness and improving seizure control [30, 31]. The identification of specific immunological signatures associated with drug sensitivity, as observed in this study, provides a rationale for exploring personalized immunomodulatory interventions to augment the efficacy of antiepileptic medications in pediatric patients. Furthermore, the lack of significant differences in demographic factors between the insensitive and sensitive groups suggests that individual variation in drug response may be influenced more by underlying pathophysiological mechanisms, such as immune dysregulation and altered seizure characteristics, rather than demographic characteristics. This underscores the heterogeneity of pediatric epilepsy and the need for comprehensive, multidimensional assessments to tailor treatment regimens to the specific needs of each patient.

While this study provides valuable insights into the interplay between immunological factors, seizure characteristics, and antiepileptic drug mechanisms in pediatric epilepsy, several limitations should be acknowledged. Firstly, the study sample size was relatively small, which may limit the generalizability of the findings to broader pediatric epilepsy populations. Additionally, the cross-sectional nature of the study restricts the establishment of causal relationships between immunological factors and drug sensitivity, warranting longitudinal investigations to elucidate the long-term impact of immune dysregulation on treatment outcomes. Furthermore, the assessment of immunological factors was confined to a select set of cytokines, and additional immunological markers or immune cell profiles could contribute further to our understanding of the immune-mediated mechanisms in pediatric epilepsy. Moreover, while efforts were made to control for confounding variables, unmeasured factors such as genetic variations and environmental influences could introduce potential biases. Future studies addressing these limitations was instrumental in enhancing our comprehension of the intricate immunological and pharmacological dynamics in pediatric epilepsy.

Conclusions

In conclusion, the findings of this study elucidate the intricate relationship between immunological factors, seizure characteristics, and antiepileptic drug sensitivity in pediatric epilepsy. The observed alterations in immunological parameters and their associations with drug responsiveness suggest a potential link between immune dysregulation and treatment outcomes in pediatric epilepsy. However, the retrospective design of this study limits the ability to draw causal inferences. These findings underscore the need for future prospective studies and experimental models to validate the mechanistic roles of cytokines in modulating ASMs responsiveness and seizure control. These findings hold implications for

advancing our understanding of the pathophysiological mechanisms underlying pediatric epilepsy and underscore the need for integrated, personalized approaches that account for the complex interplay between immune function and neuronal excitability.

Acknowledgements
The authors express their appreciation to staff in Maternity & Child Care Center of Qinhuangdao and Qinhuangdao Jianyi Hospital, for their technical assistance.

Author contributions
Dongyan Zhang: study design, data analysis, drafting the manuscript and revision of the manuscript. Hongan Sun: data collection and analysis, drafting the manuscript, investigation. All authors read and approved the final version of the manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
All data generated or analyzed in this study are included in the present manuscript.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Maternity & Child Care Center of Qinhuangdao in accordance with regulatory and ethical guidelines pertaining to retrospective research studies (Approval number: 2024-03-064). The procedures were conducted in accordance with the ethical standards set forth by the Committee on Human Experimentation and the Helsinki Declaration of 1964, as revised in 2013. Given that this retrospective study utilized de-identified patient data, there was no potential for harm or impact on patient care. Therefore, informed consent was waived. This waiver was approved by the institutional review board and ethics committee of our institution in accordance with regulatory and ethical guidelines pertaining to retrospective studies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 23 September 2024 / Accepted: 25 February 2025
Published online: 17 March 2025

References

1. Wagner J, Bhatia S, Marquis BO, Vetter I, Beatty CW, Garcia R, et al. Health disparities in pediatric epilepsy: methods and lessons learned. J Clin Psychol Med Settings. 2023;30(2):251–60.
2. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
3. Liparoti G, Burchiani B, Mencaroni E, Tripodi D, Di Cara G, Verrotti A. Individualizing doses of antiepileptic drugs. Expert Opin Drug Metab Toxicol. 2022;18(3):219–33.
4. Tolaymat A, Nayak A, Geyer JD, Geyer SK, Carney PR. Diagnosis and management of childhood epilepsy. Curr Probl Pediatr Adolesc Health Care. 2015;45(1):3–17.
5. Singhi S, Gupta A. A review of the selected and newer Antiseizure medications used in childhood epilepsies. Indian J Pediatr. 2021;88(10):993–9.
6. Sanz P, Rubio T, Garcia-Gimeno MA. Neuroinflammation and epilepsy: from pathophysiology to therapies based on repurposing drugs. Int J Mol Sci. 2024;25(8).
7. von Rüden EL, Potschka H, Tipold A, Stein VM. The role of neuroinflammation in canine epilepsy. Veterinary journal (London, England: 1997). 2023;298–299:106014.
8. Chen TS, Lai MC, Huang HI, Wu SN, Huang CW, Immunity. Ion Channels Epilepsy Int J Mol Sci. 2022;23(12).
9. Fortunato F, Giugno A, Sammarra I, Labate A, Gambardella A. Epilepsy, immunity and neuropsychiatric disorders. Curr Neuropharmacol. 2023;21(8):1714–35.
10. Flammer J, Neziraj T, Rüegg S, Pröbstel AK. Immune mechanisms in epileptogenesis: update on diagnosis and treatment of autoimmune epilepsy syndromes. Drugs. 2023;83(2):135–58.
11. Gonzalez-Giraldo E, Sullivan JE. Advances in the treatment of Drug-Resistant pediatric epilepsy. Semin Neurol. 2020;40(2):257–62.
12. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58(4):522–30.
13. Soltani Khaboushan A, Yazdanpanah N, Rezaei N. Neuroinflammation and Proinflammatory cytokines in epileptogenesis. Mol Neurobiol. 2022;59(3):1724–43.
14. Suleymanova EM. Behavioral comorbidities of epilepsy and neuroinflammation: evidence from experimental and clinical studies. Epilepsy Behavior: E&B. 2021;117:107869.
15. Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nat Reviews Neurol. 2019;15(8):459–72.
16. Maddipati KR. Non-inflammatory physiology of inflammatory Mediators - Unalamation, a new paradigm. Front Immunol. 2020;11:580117.
17. Cunha-Reis D, Caulino-Rocha A, Correia-de-Sá P. VIPergic neuroprotection in epileptogenesis: challenges and opportunities. Pharmacol Res. 2021;164:105356.
18. Ma H, Lin H. Advances regarding neuroinflammation biomarkers with noninvasive techniques in epilepsy. Behav Neurol. 2021;2021:7946252.
19. Pracucci E, Pillai V, Lamers D, Parra R, Landi S. Neuroinflammation: A signature or a cause of epilepsy?? Int J Mol Sci. 2021;22(13).
20. Ravizza T, Scheper M, Di Sapia R, Gorter J, Aronica E, Vezzani A. mTOR and neuroinflammation in epilepsy: implications for disease progression and treatment. Nat Rev Neurosci. 2024;25(5):334–50.
21. Miziak B, Konarzewska A, Ułamek-Kozioł M, Dudra-Jastrzębska M, Pluta R, Czuczwar SJ. Anti-Epileptogenic effects of antiepileptic drugs. Int J Mol Sci. 2020;21(7).
22. Perucca E. Antiepileptic drugs: evolution of our knowledge and changes in drug trials. Epileptic Disorders: Int Epilepsy J Videotape. 2019;21(4):319–29.
23. Zelleke T, Pasupuleti A, Depositario-Cabacar D, Kao A. Antiepileptic drugs in pediatrics. Handb Exp Pharmacol. 2020;261:1–24.
24. Karaźniewicz-Łada M, Główka AK, Mikulska AA, Główka FK. Pharmacokinetic Drug-Drug interactions among antiepileptic drugs, including CBD, drugs used to treat COVID-19 and nutrients. Int J Mol Sci. 2021;22(17).
25. Peng A, Lai W, Li W, Qiu X, Zhang L, He S, Chen L. Antiepileptic drugs for acute encephalitic patients presented with seizure. Epilepsy Res. 2020;164:106347.
26. Husari KS, Dubey D. Autoimmune epilepsy. Neurotherapeutics: J Am Soc Experimental Neurother. 2019;16(3):685–702.
27. Li X, Guo Q, Zheng Z, Wang X, Liu S. Immune-mediated epilepsy with GAD65 antibodies. J Neuroimmunol. 2020;341:577189.
28. Mukhtar I. Inflammatory and immune mechanisms underlying epileptogenesis and epilepsy: from pathogenesis to treatment target. Seizure. 2020;82:65–79.
29. Foiadelli T, Santangelo A, Costagliola G, Costa E, Scacciati M, Riva A, et al. Neuroinflammation and status epilepticus: a narrative review unraveling a complex interplay. Front Pediatr. 2023;11:1251914.
30. Sun H, Ma D, Cheng Y, Li J, Zhang W, Jiang T, et al. The JAK-STAT signaling pathway in epilepsy. Curr Neuropharmacol. 2023;21(10):2049–69.
31. Tripathi S, Nathan CL, Tate MC, Horbinski CM, Templer JW, Rosenow JM et al. The immune system and metabolic products in epilepsy and glioma-associated epilepsy: emerging therapeutic directions. JCI Insight. 2024;9(1).

Publisher's note