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Molecular & Cellular Biomechanics 2025, 22(2), 740.
https://doi.org/10.62617/mcb740

Article

Correlation analysis between MTHFR gene C677T polymorphism, serum apolipoprotein E concentration, and traumatic brain injury epilepsy

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CITATION

Yin Y, Liu M, Jiang J. Correlation analysis between MTHFR gene C677T polymorphism, serum apolipoprotein E concentration, and traumatic brain injury epilepsy. Molecular & Cellular Biomechanics. 2025; 22(2): 740. https://doi.org/10.62617/mcb740

ARTICLE INFO

Received: 7 November 2024
Accepted: 26 November 2024
Available online: 25 January 2025

Abstract: Objective: This study investigates the correlation between the methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism, serum apolipoprotein E (ApoE) concentration, and the risk of epilepsy following traumatic brain injury (TBI), aiming to identify potential biomarkers for early diagnosis and intervention. **Methods:** A total of 60 patients with post-traumatic epilepsy (observation group) and 60 healthy controls were included. Serum ApoE concentrations were measured using enzyme-linked immunosorbent assay (ELISA), and MTHFR C677T polymorphisms were analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Statistical analysis included binary logistic regression to identify independent risk factors and Spearman rank correlation to evaluate relationships between variables. **Results:** Serum ApoE levels were significantly higher in the observation group (36.26 ± 6.16 mg/L) compared to controls (30.19 ± 5.27 mg/L, $P < 0.001$). The frequency of the TT genotype and C allele was also markedly elevated in the observation group (TT: 41.67% vs. 8.33%; C allele: 56.67% vs. 31.67%, both $P < 0.05$). Logistic regression analysis identified TT genotype (OR = 6.271, $P < 0.001$) and elevated ApoE levels (OR = 6.572, $P < 0.001$) as independent risk factors. A positive correlation between ApoE levels and the TT genotype was observed ($r = 0.629$, $P < 0.001$). **Conclusion:** The MTHFR C677T polymorphism and serum ApoE concentration are strongly associated with epilepsy after TBI. These findings suggest that they could serve as biomarkers for early identification of high-risk individuals, paving the way for targeted prevention and management strategies.

Keywords: traumatic epilepsy; craniocerebral injury; apolipoprotein E; methylene tetrahydrofolate reductase; genetic polymorphism

1. Introduction

Traumatic epilepsy has emerged as a significant concern within the medical community, particularly in the realm of neurology and neurosurgery. The occurrence of secondary epileptic seizures following craniocerebral injuries is a complex and often debilitating phenomenon. Traumatic epilepsy primarily refers to the secondary epileptic seizures that occur following craniocerebral injuries, driven by brain tissue damage from cerebral vascular or brain parenchyma injuries, leading to local cerebral scars, cerebral atrophy, and other epileptogenic lesions, ultimately causing epilepsy [1,2]. Craniocerebral injuries can result from a multitude of causes, including but not limited to motor vehicle accidents, falls, sports-related traumas, and violent assaults. These injuries inflict direct damage to the brain tissue, disrupting the delicate balance of the central nervous system. The damage to the

cerebral vascular system can lead to hemorrhage and subsequent ischemia, while injury to the brain parenchyma can cause neuronal death and axonal damage. These initial insults set off a cascade of events that ultimately lead to the formation of local cerebral scars and cerebral atrophy. The scar tissue disrupts the normal electrical activity of the brain, creating an environment conducive to the generation of epileptic seizures. As a common complication of craniocerebral injury, traumatic epilepsy has far-reaching consequences for patients. It can exacerbate the existing brain damage by promoting cerebral edema. The accumulation of fluid within the brain parenchyma increases intracranial pressure, further compromising the already damaged tissue. This, in turn, leads to cerebral hypoxia-ischemia, as the blood supply to the brain is restricted. The combination of these factors not only aggravates the cerebral tissue injury but also significantly increases the risk of death and the occurrence of cerebral herniation, a life-threatening condition where parts of the brain are displaced due to increased intracranial pressure. Beyond the immediate physical threats, traumatic epilepsy has a profound impact on the life and survival quality of patients [3–5]. Patients often experience recurrent seizures, which can limit their mobility, independence, and ability to engage in daily activities. The fear of having a seizure in public can lead to social isolation and psychological distress. Cognitive impairments, such as memory loss, attention deficits, and difficulties with learning and problem-solving, are also common. These factors can have a detrimental effect on patients' educational and occupational opportunities, further reducing their quality of life. In recent years, there has been a growing interest in understanding the genetic and molecular underpinnings of traumatic epilepsy. Recent studies have indicated that variations in serum lipoprotein E and MTHFR gene C677T and the occurrence and progression of craniocerebral injury epilepsy are significantly correlated [6]. Serum lipoprotein E is a major lipoprotein in the brain, primarily maintaining the integrity of microtubular structures in neurons [7]. Microtubules are essential for intracellular transport, providing a framework for the movement of organelles and vesicles within the neuron. Disruption of these microtubular structures can lead to abnormal neuronal function and increased susceptibility to epileptic seizures. The role of serum lipoprotein E in this context is an area of active research, as alterations in its levels may reflect changes in the brain's microenvironment and its ability to repair and maintain neuronal integrity. MTHFR, or methylenetetrahydrofolate reductase, is an enzyme that occupies a key position in the folate metabolism pathway. MTHFR is primarily located on chromosome 1p36.3, and is a rate-limiting enzyme. Variants of its C677T gene due to reduced activity and enzyme thermostability are prone to increase the risk of craniocerebral injury epilepsy [8]. The C677T variant leads to an amino acid substitution, which affects the enzyme's function. This alteration can disrupt the normal folate metabolism, leading to increased levels of homocysteine and decreased levels of important metabolites such as S-adenosylmethionine. These changes can have a negative impact on the methylation status of DNA and proteins, which is crucial for normal brain development and function. The resulting changes in the brain's epigenetic landscape may contribute to the development and progression of epileptogenic lesions. Given the potential significance of these genetic and molecular factors in the pathogenesis of traumatic epilepsy, the present study was designed to

further investigate their relationship. We selected 60 patients with craniocerebral injury epilepsy admitted to our hospital for research. To measure the serum lipoprotein E concentration, we applied the enzyme-linked immunosorbent assay (ELISA). This technique offers high sensitivity and specificity, allowing for accurate quantification of the lipoprotein levels in the patients' sera. By obtaining these measurements, we aimed to determine whether there were any significant differences in serum lipoprotein E levels between patients with traumatic epilepsy and healthy controls, as well as to explore any potential correlations with disease severity and progression.

In addition, we employed polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP) to compare the polymorphism of MTHFR gene C677T. This method enables us to detect the presence of the C677T variant at the genetic level. By analyzing the frequency and distribution of this variant in our patient population, we hoped to gain insights into its role in the development of traumatic epilepsy. Understanding the genetic susceptibility conferred by the MTHFR C677T variant could potentially help in identifying patients at high risk and developing personalized preventive and therapeutic strategies.

This study aimed to explore the correlation between the serum lipoprotein E concentration and polymorphism of MTHFR gene C677T and the occurrence and progression of craniocerebral injury epilepsy. By conducting this research, we hoped to contribute to the existing body of knowledge and provide a foundation for future studies aimed at improving the diagnosis, treatment, and prognosis of patients with traumatic epilepsy. The results of this study are reported below, with the intention of shedding light on these important aspects of traumatic epilepsy and potentially opening new avenues for research and clinical intervention.

2. Materials and methods

2.1. General information

The 60 patients with traumatic brain injury epilepsy who were admitted to our hospital from April 2022 to April 2023 were included in the study as the observation group. The inclusion criteria were: (1) patients with typical clinical manifestations of epilepsy and abnormal pathological epileptiform waves on electroencephalography; (2) patients with a history of traumatic brain injury before the onset of epilepsy; (3) patients who had experienced at least two seizures. The exclusion criteria were: (1) patients with epilepsy caused by primary disease or familial history or genetic disease; (2) patients with systemic diseases, central nervous system diseases, or mental diseases. We also enrolled 60 healthy individuals who were undergoing routine physical examination at our hospital during the same period as the observation group. The control group consisted of 33 males and 27 females, aged 18 to 70 years, with a mean age of (36.25 ± 2.34) years; 22 patients underwent surgical treatment for epilepsy, while 38 patients were treated with pharmacological agents. The observation group consisted of 36 males and 24 females, aged 20 to 72 years, with a mean age of (37.48 ± 2.46) years; 25 patients underwent surgical treatment for epilepsy, while 35 patients were treated with pharmacological agents. This study was approved by the Ethics Committee of our hospital and implemented after obtaining

informed consent from patients and their families and signing relevant paper consent forms. The baseline characteristics of the two groups were similar, with no significant differences ($P > 0.05$), and thus they were comparable.

2.2. Methods

2.2.1. Detection of serum apolipoprotein E concentration

In the early morning, a precisely measured volume of 4 mL of peripheral venous blood was carefully collected from each and every participant. The collected blood samples were then promptly and gently placed into tubes that already contained the appropriate anticoagulants to prevent clotting. Subsequently, these samples were subjected to a centrifugation process at a speed of 3500 revolutions per minute for a duration of 15 minutes, with a centrifuge radius of 12 cm. This process effectively separated the serum from the other components. To determine the concentration of serum Apolipoprotein E, an enzyme-linked immunosorbent assay (ELISA) was employed. The assay was carried out meticulously, strictly adhering to the detailed protocol provided by the manufacturer to ensure accurate and reliable results.

2.2.2. Detection of gene polymorphism

Peripheral venous blood (4 mL) was collected from participants in the early morning to ensure optimal sample integrity. DNA extraction was conducted using the chloroform-saturated phenol method, which effectively separates DNA from proteins and other cellular components, yielding high-purity genomic DNA. The analysis of the MTHFR gene C677T polymorphism was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). This technique amplifies the specific gene segment and then utilizes restriction enzymes to cut the DNA at specific sites, allowing for the identification of different genetic variants based on the resulting fragment patterns.

2.3. Statistical analysis

The comprehensive statistical analysis of the collected data was carried out with the utilization of the SPSS 26.0 software. For the count data, which represented the frequencies and proportions of various categorical variables, they were presented in the format of [n(%)]. To evaluate the differences between groups in terms of these count data, the Chi-square test was applied. Regarding the data that adhered to the criteria of normal distribution and homoscedasticity, they were expressed as mean ± standard deviation ($\bar{x} \pm s$). Paired sample t-tests were employed to compare the data within the same group at different time points or under different conditions. Meanwhile, independent sample t-tests were utilized to make comparisons between different groups. To further explore and identify the potential risk factors contributing to traumatic brain injury epilepsy, a binary logistic regression analysis was performed. Additionally, the Spearman rank correlation analysis was utilized to meticulously analyze the correlation between the concentration of serum Apolipoprotein E, the MTHFR gene C677T polymorphism, and the occurrence of traumatic brain injury epilepsy. The significance level was set at $P < 0.05$, which denoted a statistically significant difference.

3. Results

3.1. Comparison of the frequency of MTHFR gene C677T and AA/AG genotypes and serum apolipoprotein E concentration between the two groups

There was no statistical significance difference in the frequency of CT genotype between the two groups ($P > 0.05$); compared to the control group, the serum apolipoprotein E concentration in the observation group was significantly higher, and the frequency of TT genotype and C allele was significantly higher, indicating a significant statistical difference ($P < 0.05$). The results are shown in **Table 1**.

Table 1. Comparisons between the homozygous MTHFR gene C677T allele and genotype with the plasma concentration of serum lipoprotein E ($\bar{x} \pm s$) [n(%)] in the two groups.

Group	Sample Size	ApoE(mg/L)	Genotype			Allele	
			CC	CT	TT	C	T
Observation Group	60	36.26 ± 6.16	17(28.33)	18(30.00)	25(41.67)	34(56.67)	26(43.33)
Control Group	60	30.19 ± 5.27	36(60.00)	19(31.67)	5(8.33)	19(31.67)	41(68.33)
t/χ^2		5.800	12.199	0.039	17.778	7.604	
P		0.000	0.001	0.843	0.000	0.006	

3.2. Logistic regression analysis between two groups of MTHFR gene C677T different locus genotypes and serum apolipoprotein E concentration and traumatic brain injury epilepsy

Logistic regression analysis results indicate that TT genotype and serum lipoprotein E are independent factors influencing traumatic brain injury epilepsy, with a significant difference ($P < 0.05$) as shown in **Table 2**.

Table 2 presents the genotypes of the MTHFR C677T polymorphism in two groups and the concentration of serum apolipoprotein E (ApoE) with Logistic regression analysis in patients with cerebral concussion epilepsy.

Table 2. Logistic regression analysis between two groups of MTHFR gene C677T different locus genotypes and serum apolipoprotein E concentration and traumatic brain injury epilepsy.

Indicators	β	S.E	Wald	OR	95%CI	P
CT	1.783	1.768	1.016	1.138	0.672~2.157	0.072
TT	1.374	0.412	11.122	6.271	4.149~10.841	0.000
ApoE	1.429	0.401	12.701	6.572	4.284~11.427	0.000

Note: β (Beta Coefficient): Reflects the direction and strength of the association between the independent variable and the dependent variable. A positive β indicates a positive association, while a negative β indicates an inverse association.
S.E (Standard Error): Measures the accuracy of the β coefficient estimation. Smaller values indicate more precise estimates.
Wald (Wald Test Statistic): Used to determine the significance of individual predictors in the model.
OR (Odds Ratio): Represents the likelihood of an event occurring (e.g., epilepsy) in the presence of a specific variable (e.g., TT genotype). An OR > 1 indicates an increased likelihood, while OR < 1 indicates a decreased likelihood.
95% CI (Confidence Interval): Provides the range within which the true OR is expected to fall 95% of the time. If the CI does not include 1, the result is statistically significant.
P (P-value): Indicates the statistical significance of the predictor. A P-value < 0.05 is considered significant.

3.3. Correlation analysis between MTHFR gene C677T allele and genotype and serum Apolipoprotein E concentration and traumatic brain injury epilepsy

The Spearman rank correlation analysis results showed a positive correlation between serum Apolipoprotein E concentration and TT genotype and traumatic brain injury epilepsy, with a statistically significant difference ($P < 0.05$). This is shown in **Table 3**.

Table 3. Correlation analysis between MTHFR gene C677T allele and genotype and serum Apolipoprotein E concentration and traumatic brain injury epilepsy.

Indicators	Head trauma epilepsy	
	r	***P***
ApoE	0.671	0.000
CC	0.411	0.070
CT	0.427	0.061
TT	0.629	0.000
C	0.416	0.068
T	0.398	0.071

4. Discussion

4.1. Clinical status and correlation of traumatic epilepsy

The occurrence of cerebral trauma epilepsy in patients can aggravate neural biochemical changes and pathological damage to the brain tissue, posing a severe threat to patients' life and health [9,10]. However, currently, there is no consensus among clinicians regarding the mechanisms of cerebral trauma epilepsy onset and progression. Numerous studies have suggested that cerebral trauma epilepsy is associated with variations in plasma lipid protein E concentration and MTHFR gene C677T polymorphism, and these relationships can be utilized to predict the onset and progression of the disease [11,12].

4.2. Background knowledge of plasma lipoproteins and MTHFR gene

Plasma lipoproteins are mainly synthesized by astrocytes and are encoded by three alleles from the same gene locus located at chromosome 19 [13]. There are six main genotypes, which collectively contribute to the transport of phospholipids and cholesterol in neurons [14]. MTHFR gene is located at chromosome 1p36.3, and it has been suggested that a C to T substitution at the 677th position of the gene will lead to a replacement of the amino acid valine by the amino acid alanine in MTHFR enzyme, thereby reducing the enzyme's thermostability and activity, and increasing the risk of cerebral trauma epilepsy [15–17].

4.3. Findings and analysis of this study

In this study, by detecting the serum lipoprotein E concentration and MTHFR gene C677T polymorphism in patients with head injury epilepsy, we found that the

serum lipoprotein E concentration was significantly higher than in normal physical examinations, and the TT genotype and C allele frequency were also significantly higher. This suggests that the serum lipoprotein E concentration in patients with head injury epilepsy is abnormally elevated, possibly due to the significant role of serum lipoprotein E as a multifunctional molecule in cellular signaling, stabilizing microtubule structures, and amyloid protein accumulation and clearance. It can effectively promote neural function recovery and neuron structure repair, closely related to the prognosis of head trauma [18,19]. Lipoprotein E (ApoE) is a critical protein involved in lipid metabolism and neuronal repair mechanisms. Elevated levels of serum lipoprotein E in patients with head injury epilepsy indicate that this molecule may play a protective role in the aftermath of brain injuries. The presence of higher concentrations of ApoE suggests that the body is attempting to counteract the damage caused by traumatic events. ApoE's ability to stabilize microtubule structures is particularly important, as microtubules are essential for maintaining the integrity of neuronal cells. When these structures are compromised due to trauma, the subsequent dysfunction can lead to various neurological issues, including epilepsy. Moreover, ApoE is involved in the clearance of amyloid proteins, which are associated with neurodegenerative diseases. Its role in the accumulation and clearance of these proteins implies that elevated levels of ApoE may also be a response to neuroinflammatory processes triggered by head injuries. This multifaceted role of serum lipoprotein E highlights its importance in both the immediate response to brain injury and the longer-term recovery processes. By promoting neural function recovery and facilitating structural repair, ApoE may significantly influence the prognosis of individuals suffering from head trauma. Meanwhile, MTHFR is crucial for homocysteine metabolism, and mutations at the C677T locus will lead to a decrease in stability, causing abnormal homocysteine metabolism and accumulation in the body, leading to head injury epilepsy. This significantly affects the prognosis [3,5,20,21]. The MTHFR gene encodes an enzyme responsible for converting homocysteine to methionine, an essential amino acid [22,23]. Mutations at the C677T locus can impair this enzymatic function, resulting in elevated levels of homocysteine in the bloodstream. High homocysteine levels are associated with various neurological disorders, including epilepsy, as they can contribute to neuronal excitability and neurotoxicity [24]. The relationship between MTHFR polymorphisms and head injury epilepsy underscores the importance of genetic factors in the development of neurological conditions. Individuals with the TT genotype may be at a higher risk due to impaired homocysteine metabolism, leading to increased susceptibility to seizures and other post-traumatic complications. This genetic predisposition highlights the need for personalized approaches in managing patients with head injuries, taking into account their genetic backgrounds [25].

Additionally, logistic regression analysis results revealed that TT genotype and serum lipoprotein E are independent factors affecting head injury epilepsy, and further Spearman rank correlation analysis showed that head injury epilepsy is positively correlated with serum lipoprotein E concentration and TT genotype. This suggests that MTHFR gene C677T polymorphism and serum lipoprotein E concentration are closely related to head injury epilepsy, and abnormal variations in

their levels may be risk factors for head Injury epilepsy. The findings of this study emphasize the significance of both genetic and biochemical factors in understanding the pathophysiology of head injury epilepsy. The identification of serum lipoprotein E and the MTHFR C677T polymorphism as independent risk factors provides valuable insights for clinicians. These markers can potentially guide the development of targeted therapeutic strategies aimed at mitigating the risk of epilepsy following head trauma. Furthermore, the positive correlation between serum lipoprotein E concentration and the TT genotype highlights the interplay between genetic predisposition and biochemical responses in the context of head injury. This relationship suggests that monitoring serum lipoprotein E levels could be beneficial in predicting the likelihood of developing epilepsy in patients with head injuries, allowing for earlier interventions and more effective management strategies. In summary, this study sheds light on the complex interactions between serum lipoprotein E concentration, MTHFR gene C677T polymorphism, and the risk of head injury epilepsy. The elevated levels of lipoprotein E and the presence of the TT genotype indicate potential pathways through which head injuries may lead to the development of epilepsy. Further research is needed to explore the underlying mechanisms and to evaluate the potential for these biomarkers to inform clinical practice in the management of patients with head injuries. By understanding these relationships, we can enhance our approaches to prevention and treatment, ultimately improving outcomes for individuals affected by head injury epilepsy.

4.4. Summary and outlook of the study

In summary, the serum concentration of serum lipoprotein E, the heterozygote of the MTHFR gene C677T, and the frequency ratio of genotypes in patients with head trauma epilepsy all significantly increase. Furthermore, the fluctuations of these parameters are positively correlated with the occurrence of head trauma epilepsy, suggesting that they can be used as a reference indicator for evaluating head trauma. However, this study still has certain limitations. The MTHFR gene included in the study involves only the C677T single locus, which cannot represent the entire gene. The occurrence of the disease is a result of the complex interaction of genetic and environmental factors. Future research can encompass multiple dimensions and large-scale studies on this topic [26]. The findings of this study underscore the importance of serum lipoprotein E and the MTHFR gene C677T polymorphism in the context of head trauma epilepsy. The significant increase in serum lipoprotein E concentration among patients suggests its potential role as a biomarker for assessing the severity and prognosis of head injuries. Lipoprotein E is known for its multifaceted roles in the central nervous system, including its involvement in lipid metabolism, neuronal repair, and neuroinflammation. Elevated levels of this protein may indicate an adaptive response to neuronal damage, aiming to facilitate recovery and mitigate the adverse effects of traumatic brain injury. Moreover, the heterozygote status of the MTHFR gene C677T polymorphism was found to correlate with increased susceptibility to head trauma epilepsy. This genetic variation can lead to impaired homocysteine metabolism, resulting in elevated homocysteine levels in the blood. High homocysteine concentrations have been implicated in various

neurological disorders, including epilepsy, due to their neurotoxic effects [27,28]. The identification of the MTHFR C677T polymorphism as a significant factor in head trauma epilepsy highlights the need for genetic screening in patients who have sustained head injuries. Understanding an individua's genetic predisposition can inform clinical decisions and guide preventive measures.

The positive correlation between serum lipoprotein E concentration, MTHFR C677T polymorphism, and the occurrence of head trauma epilepsy suggests that these biomarkers could serve as reference indicators for evaluating head trauma. Clinicians may benefit from monitoring these parameters to assess the risk of developing epilepsy following a head injury. Early identification of at-risk individuals could facilitate timely interventions, potentially improving patient outcomes [29,30]. Despite the promising findings, this study is not without limitations. One significant limitation is that it focused solely on the C677T single locus of the MTHFR gene. While this locus has been extensively studied, it does not encompass the entire genetic landscape of the MTHFR gene. Other polymorphisms within the MTHFR gene may also contribute to variations in homocysteine metabolism and influence the risk of head trauma epilepsy. Future studies should consider a more comprehensive analysis of the MTHFR gene, including multiple loci and their interactions. Additionally, the occurrence of head trauma epilepsy is influenced by a complex interplay of genetic and environmental factors. While this study provides valuable insights into the relationship between serum lipoprotein E, MTHFR C677T polymorphism, and head trauma epilepsy, it is essential to recognize that these factors do not operate in isolation. Environmental influences, such as the severity of the head injury, pre-existing medical conditions, and lifestyle factors, also play a crucial role in the development of epilepsy. Future research should aim to include a broader range of variables, encompassing both genetic predispositions and environmental exposures.

To enhance the robustness of the findings, large-scale studies involving diverse populations are necessary. Such studies can help validate the observed associations and explore potential variations across different demographic groups. Additionally, longitudinal studies that follow patients over time would provide insights into how serum lipoprotein E levels and MTHFR polymorphisms influence the long-term outcomes of head trauma patients. Understanding these dynamics can lead to the development of targeted therapeutic strategies and preventive measures tailored to individual patients. Moreover, future research could explore the underlying mechanisms connecting serum lipoprotein E and MTHFR C677T polymorphism to head trauma epilepsy. Investigating the biological pathways involved in these relationships may uncover novel targets for intervention. For instance, understanding how elevated lipoprotein E levels contribute to neuronal repair and recovery could inform the development of therapies aimed at enhancing these processes. Similarly, elucidating the mechanisms by which MTHFR polymorphisms affect homocysteine metabolism could lead to strategies for mitigating the associated risks.

In conclusion, the findings of this study highlight the significance of serum lipoprotein E concentration and MTHFR gene C677T polymorphism as potential biomarkers for evaluating head trauma epilepsy. The positive correlations observed suggest that these factors may play a crucial role in the pathophysiology of the

condition. However, the limitations of the study, particularly the focus on a single locus of the MTHFR gene and the complex interplay of genetic and environmental factors, emphasize the need for further research. Future studies should adopt a multidimensional approach, incorporating larger sample sizes and diverse populations to enhance the understanding of head trauma epilepsy. By addressing these gaps, researchers can contribute to the development of effective strategies for prevention, diagnosis, and treatment, ultimately improving the quality of life for individuals affected by head trauma and its associated complications.

Author contributions: Conceptualization, YY and ML; methodology, ML and JJ; software, ML and JJ; validation, YY, ML and JJ; formal analysis, YY and ML; investigation, JJ; resources, YY; data curation, YY; writing—original draft preparation, YY; writing—review and editing, ML and JJ; visualization, YY and ML; supervision, JJ; project administration, YY. All authors have read and agreed to the published version of the manuscript.

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Second People's Hospital of Longgang District (No.: 201906009370001040, date: 13 March 2024).

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

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