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Research article

Is the regulation of lamotrigine on depression in patients with epilepsy related to cytokines?

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ABSTRACT

Objectives: The purpose of this study was to analyze the effects of lamotrigine on peripheral blood cytokines and depression in patients with epilepsy and to explore the possible mechanism by which lamotrigine regulates depression in patients with epilepsy.

Methods: 50 healthy people, 72 patients treated with lamotrigine (LTG group) and 72 patients treated with valproate were enrolled (VPA group). Cytokine levels in the peripheral blood of the subjects were measured and their level of depression was scored according to the self-rating Depression Scale (SDS), Hamilton Depression Scale (HAMD) and Chinese version of Epilepsy Depression Scale (c-NDDI-E). The cytokine levels and depression scale scores were compared between the three groups. The correlation between cytokine levels and depression scale scores was analyzed.

Results: The levels of IL-1β, IL-2, IL-6, and TNF-α and the SDS, HAMD, and c-NDDI-E scores in healthy group was lower than that in epileptic group. After 6 months of treatment, the difference valule of IL-1β、IL-6、TNF-α、SDS and HAMD before and after treatment in LTG group significantly higher than that in VPA group. Correlation analysis showed that the SDS scores were correlated with the levels of IL-1β and TNF-α, and the HAMD scores were correlated with the levels of TNF-α. Multiple linear regression analysis showed that the HAMD scores were correlated with the levels of TNF-α.

Conclusion: Lamotrigine can inhibit peripheral blood inflammation and improve depression in epileptic patients. Lamotrigine improved depressive mood in epileptic patients, which may be related to reduced TNF-α levels.

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1. Introduction

Epilepsy is a common disease of the nervous system, repeated seizures of epilepsy bring huge economic burden to individuals and society [1]. In recent years, the total number of epilepsy patients worldwide can be as high as 70 million. Approximately 2.4 million people worldwide are newly diagnosed with epilepsy each year [2]. Recurrent seizures of epilepsy affect the quality of life of patients with epilepsy, including the economy, education, marriage, work and other aspects.

The pathogenesis of epilepsy is not clear, and previous studies have suggested that seizures in epilepsy are related to structural changes, genetics, infection, metabolism and other reasons [3–5]. In 2017, immune factors were recognized as important causes of seizures by the International League against Epilepsy, and the role of autoimmune factors in the pathogenesis of epilepsy is gaining increasing attention [6]. At present, an increasing number of studies have suggested that immune disorders and inflammatory factors participate in the pathophysiological mechanism of epilepsy, promoting recurrent seizures [7]. In a number of clinical trials, traditional antiepileptic drugs such as carbamazepine, sodium valproate and phenytoin sodium have been confirmed to significantly affect the levels of cytokines in epileptic patients [8]. Lamotrigine (LTG) has also been shown to inhibit IL-1β, IL-6, and TNF-α secretion in mice in LPS/conA-induced inflammatory models [9]. In AD mouse model, LTG has been shown to inhibit cytokine secretion such as IL-1 β and IL-6, and improve the brain inflammatory response of AD mice. However, until now, there has been a lack of studies on the correlation between the new antiepileptic drug LTG and cytokines in patients with epilepsy. By comparing the changes in cytokine levels before and after LTG treatment in patients with epilepsy, this study explored whether LTG was related to peripheral blood cytokines in epileptic.

Epilepsy is associated with many comorbidities, which seriously worsens the prognosis of epilepsy patients [10]. Among them, depression is the most common emotional disorder in epilepsy patients, and the harm is great. Clinical studies have indicated that incidence of depression is up to 12.7–36.5 % in children with epilepsy [11]. Epilepsy combined with depression can seriously affect the quality of life of epileptic patients. In addition, depression leads to a much higher suicide rate in epileptic patients, thus significantly increasing the risk of death in epilepsy patients [12]. In previous studies, LTG was thought to have a regulatory effect on depressive mood [13,14], but the mechanism is unclear. This study observed the changes in peripheral blood cytokines and depressive mood in epileptic patients before and after LTG treatment and analyzed their correlation to explore the possible mechanism by which LTG regulates depression in epileptic patients. To search for possible biomarkers and potential therapeutic targets in patients with epilepsy complicated by depression.

2. Methods

2.1. Research objects

Clinical data of 643 epilepsy patients who visited the Department of Neurology, Affiliated Hospital of Xuzhou Medical University from October 2020 to July 2022 were collected. 120 patients were treated with lamotrigine (specification: 25 mg, manufacturer: GlaxoSmithKline Pharmaceuticals S. A.) as monotherapy according to their seizure conditions. Among them, 48 patients stopped LTG or combined it with other antiepileptic drugs within 6 months, and the remaining 72 patients with epilepsy were enrolled as the study subjects (LTG group). According to the same method, 72 epileptic patients who received valproate (specification: 25 mg, manufacturer: Sanofi (Hangzhou) Pharmaceutical Co., LTD) monotherapy were selected as the study subjects (VPA group). Fifty healthy subjects from the physical examination center of our hospital were selected as the healthy control group. Our study subjects were all from the same region, with similar diets, habits, climate, etc., to minimize the interference of the above factors on the results.

Inclusion criteria: ① compared with the diagnostic criteria defined by the International League against Epilepsy (ILAE) in 2017, the diagnosis of epilepsy could be confirmed by clinical manifestations, EEG or cranial MRI results; ② patients could cooperate during the depression self-rating scale examination; ③ patients were informed and consented to this study; ④ lamotrigine or valproate was administered as monotherapy for 6 months.

Exclusion criteria: ① patients that had other chronic diseases with a significant influence on depression; ② patients hat had a seizure within 72 h; ③ in addition to epilepsy, there were other organic neuropsychiatric diseases in the brain; ④ patients that had a long history of alcoholism or psychoactive substance abuse; ⑤ patients that used hormones and other immunosuppressants within 6 months; ⑥ patients with other autoimmune, neoplastic or inflammatory diseases; ⑦ patients with an inability to cooperate during the depression self-rating scale examination; ⑧ there was no history of other psychotropic drug use during the study period.

This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (approval No. XYFY2021-KL281-01). All subjects knew the purpose of the study in advance and signed the informed consent form.

2.2. Research method

Detailed medical histories were collected for all patients, including name, sex, age, age at onset, course of disease, type of seizure, antiepileptic drug use, head imaging, electroencephalogram, therapeutic effectiveness etc. At the same time, the subjects were evaluated by a depression scale. In the early morning of the same day as the depression scale assessment, subjects were provided with hematological samples while fasting. The levels of IL-1β, IL-2, IL-6, and TNF-α in the peripheral blood of epileptic patients were determined by multimmicrosphere flow cytometry (The detection limits is 0.11 pg/ml, Coefficient of variation (CV) $\leq$ 15 %). Peripheral blood cytokine levels and depression scale were measured before and 6 months after treatment. The peripheral blood cytokine levels and depression scale scores of epileptic patients were compared between the three groups, and the LTG group and VPA group

were compared before and 6 months after treatment. The correlation between cytokine levels and depression scale scores was analyzed.

2.3. Efficacy evaluation

The average monthly frequency of seizures 3 months before starting the drug was compared with the average monthly frequency of seizures 6 months after treatment, and the efficacy was divided into no seizures (no seizures of any type), control (seizure frequency reduction ≥75 %), significant (seizure frequency reduction <75 %, ≥50 %), and ineffective (seizure frequency reduction <50 %).

2.4. Methods for the detection of peripheral blood cytokines

The detection methods used in this study are described as follows. The levels of cytokine were detected by multimicrosphere flow cytometry, and 5 ml of peripheral venous blood was collected with EDTA anticoagulant collection. After centrifugation at 1000×*g* for 10 min, the isolated plasma was taken for testing. Then, 25 μL of test buffer and 25 μL of matrix B were added to the sample tube and calibration tube, and 25 μL of sample and calibrator were added. After mixing well, 25 μL was added to all tubes for trapping microsphere antibody and 25 μL for detecting antibody and incubated at room temperature for 2 h (400 r/min) by shock and shading. Then, 25 μL SA-PE was added to all tubes and incubated at room temperature and away from light for 0.5 h. Then, 500 μL 1 × washing buffer was added to each tube, swirled for a few seconds, and centrifuged at 400×*g* for 5 min, and the liquid was slowly poured out and inverted on the absorbent paper. According to the sample loading requirements of flow cytometer, 200 μL washing buffer was added into each tube, and the microspheres were suspended by swirling for 10 s for immediate machine detection. Use software for data analysis. The kit instructions were strictly followed (Qingdao Riskell Biotechnology Co, Ltd.).

2.5. Depression scale examination

Before and 6 months after treatment, patients with epilepsy were evaluated by the depression scale.

The Self-rating Depression Scale (SDS) [15] is described as follows. With the increase of the score, it indicates that the degree of depression is more serious. The normal upper limit of the total score of the SDS is 53; 53–62 indicates mild depression, 63–72 indicates moderate depression, and 73 or more indicates severe depression.

The Hamilton depression scale (HAMD) [16] is described as follows. The higher the score, the more severe the depressive symptoms [17].

A score >12 is classified as the cutoff value for epilepsy with depression according to the Neurologic Disorders Depression Inventory for Epilepsy (c-NDDI-E) [18].

2.6. Statistical analysis

SPSS 26.0 was used for statistical analysis of the data. The measurement data were tested for normality, and the data conforming to a normal distribution were expressed as the mean ± standard deviation ($x \pm s$). Independent sample T test was used to compare data between two groups. One-way analysis of variance was used for comparison among the three groups. Data inconsistent with a normal distribution were represented by M (Q1, Q3), and comparisons between the two groups were performed by the Mann−Whitney *U* test. Classified counting data are represented by the number of cases, Chi-square test was used for comparison between the two groups. Spearman correlation analysis is used to analyze the correlation among each index. The factors with statistical significance in

Table 1
Comparison of clinical data between VPA group, LTG group and healthy control group.

		Health group	VPA (n = 72)	LTG (n = 72)	$F/t/x^2$	*P*
gender	male	25	36	37	0.035	0.983
	female	25	36	35		
age		37.62 ± 14.44	39.72 ± 17.91	39.50 ± 16.92	0.267	0.766
Age of onset		–	33.88 ± 20.50	33.79 ± 19.54	0.029	0.554
Course of disease		–	5.83 ± 6.92	5.70 ± 6.44	0.112	0.781
Seizure type	focal	–	52	53	0.706	0.702
	Generalized	–	16	17		
	Unexplained	–	4	2		
Attack frequency	>1/week	–	18	20	0.189	0.979
	1/week −1/month	–	30	29		
	1/month-1/year	–	16	16		
	<1/year	–	8	7		
Efficacy evaluation	no seizures	–	20	21	0.116	0.990
	control	–	32	30		
	significant	–	18	19		
	ineffective	–	2	2		

Note: VPA: Sodium valproate; LTG: Lamotrigine.

univariate analysis were analyzed by multiple linear stepwise regression analysis. The significance level was set to 0.05 throughout our study.

3. Results

3.1. Comparison of clinical data between VPA group, LTG group and healthy control group

Through one-way ANOVA, two independent samples T test and *Chi-square* test, it was suggested that there was no significant difference in clinical data between the three groups ($P > 0.05$). For details, see Table 1.

3.2. Comparison of cytokine levels and depression scale scores between healthy group and epileptic group

Through Mann-Whitney *U* test, it was suggested that the levels of IL-1β, IL-2, IL-6, TNF-α and the scores of SDS, HAMD, C-NDDI-E in healthy group was significantly lower than that in epileptic group ($P < 0.05$). For details, see Table 2.

3.3. Comparison of cytokine levels between VPA group and LTG group

The difference value of IL-1 β, IL-2, IL-6 and TNF- α levels before and after treatment between the two groups were compared. Through Mann-Whitney *U* test, it was suggested that there were significant differences in the levels of IL-1 β, IL-6 and TNF- α between the two groups ($P < 0.05$). There was no significant difference in IL-2 level between the two groups ($P > 0.05$). For details, see Table 3.

3.4. Comparison of depression scale scores between the VPA group and LTG group

The difference value of SDS, HAMD, C-NDDI-E, NHS3 scores before and after treatment between the two groups were compared. Through Mann−Whitney *U* test, it was suggested that there were significant differences in the scores of SDS and HAMD between the two groups ($P < 0.05$). There was no significant difference in C-NDDI-E and NHS3 scores between the two groups ($P > 0.05$). For details, see Table 4.

3.5. Correlation analysis between depression scale scores and peripheral blood cytokines in LTG group

Spearman correlation analysis showed that SDS scores were positively correlated with IL-1β levels ($r_s = 0.535$, $P < 0.001$), TNF-α levels and SDS ($r_s = 0.237$, $P = 0.045$) and HAMD ($r_s = 0.672$, $P < 0.001$) scores were positively correlated in the pre-treatment epileptic group. SDS scores were positively correlated with IL-1β levels ($r_s = 0.638$, $P < 0.001$) and TNF-α levels ($r_s = 0.339$, $P = 0.004$) in the post-treatment epileptic group. There was no statistically significant correlation between IL-6 levels and depression scale scores. For details, see Table 5.

3.6. Multiple linear stepwise regression analysis of factors affecting depression in LTG group

The correlation indices IL-1β and TNF-α of univariate analysis were included in multiple linear regression analysis, with the difference in cytokine levels before and after treatment as the independent variable and the difference in depression scale score as the dependent variable, suggesting that HAMD (*Beta* = 0.456, $P < 0.001$) scale scores were positively correlated with TNF-α levels.

4. Discussion

In recent years, with the continuous exploration of the pathogenesis of epilepsy, the important role of immune and inflammatory factors in epileptic seizures has received increasing attention. Pro-inflammatory cytokines are crucial in a range of pathophysiological processes of epileptic seizures [19]. In this study, by comparing the levels of peripheral blood cytokines between the healthy control group and the epileptic group, it was found that the levels of IL-1β, IL-2, IL-6 and TNF-α in the epileptic group were significantly higher

Table 2
Comparison of cytokine levels and depression scale scores between healthy group and epileptic group [M (Q1, Q3); pg/mL].

	healthy group (n = 50)	epileptic group (n = 144)	*Z*	*P*
IL-1β	2.44 (1.70,3.58)	11.99 (7.57,17.22)	−9.201	<0.001[a]
IL-2	1.18 (0.59,1.56)	2.37 (0.98,4.56)	−5.273	<0.001[a]
IL-6	2.03 (1.35,2.54)	5.78 (4.14,8.20)	−8.301	<0.001[a]
TNG-α	1.39 (0.85,1.84)	4.42 (2.11,7.57)	−8.144	<0.001[a]
SDS	28.00 (26.00,30.25)	55.00 (49.25,62.00)	−10.487	<0.001[a]
HAMD	3.50 (1.75,5.25)	20.00 (16.00,28.00)	−10.444	<0.001**
C-NDDI-E	2.00 (1.75,4.00)	17.00 (15.25,20.00)	−10.582	<0.001[a]

Note.
[a] $P < 0.01$.

Table 3
Comparison of cytokine levels in peripheral blood between the VPA group and LTG group [M (Q1, Q3); pg/mL].

	VPA (n = 72)	LTG (n = 72)	*Z*	*P*
IL-1β	3.89 (1.82,6.05)	7.93 (3.29,11.66)	−3.868	< 0.001[b]
IL-2	0.65 (0.01,1.75)	0.99 (0.04,3.47)	−0.889	0.374
IL-6	1.41 (-1.97,3.48)	3.85 (0.18,9.12)	−2.967	0.003[b]
TNF-α	1.35 (0.00,2.50)	2.54 (0.04,4.61)	−2.112	0.035[a]

Note.
VPA: Sodium valproate; LTG: Lamotrigine; The cytokine value is the pre-treatment value minus the post-treatment value.
[a] $P < 0.05$.
[b] $P < 0.01$.

Table 4
Comparison of depression scale scores between the VPA group and LTG group [M (Q1, Q3)].

	VPA (n = 72)	LTG (n = 72)	*Z*	*P*
SDS	10.00 (8.00,13.00)	13.00 (7.00,19.00)	−2.189	0.029[a]
HAMD	6.00 (3.00,8.75)	12.00 (4.25,16.00)	−4.510	< 0.001[b]
C-NDDI-E	9.00 (8.00,10.00)	9.00 (6.00,12.00)	−0.268	0.789
NHS3	5.00 (2.00,6.75)	4.00 (1.25,6.00)	−0.765	0.444

Note.
VPA: Sodium valproate; LTG: Lamotrigine; The scale score is the pre-treatment value minus the post-treatment value.
[a] $P < 0.05$.
[b] $P < 0.01$.

Table 5
Correlation analysis between depression scale scores and peripheral blood cytokines in LTG group.

	IL-1β		IL-6		TNF-α	
	r_s	*P*	r_s	*P*	r_s	*P*
SDS1	0.535[a]	<0.001	0.129	0.279	0.237[a]	0.045
SDS2	0.638[a]	<0.001	0.090	0.450	0.339[a]	0.004
HAMD1	0.050	0.678	0.186	0.118	0.672[a]	<0.001
HAMD2	−0.050	0.678	0.103	0.387	−0.035	0.770

Note.
SDS1 was SDS score of the pre-treatment group. SDS2 was SDS score of the post-treatment group. HAMD1 was the HAMD score of the pre-treatment group. HAMD2 was the HAMD score of the post-treatment group.
[a] $P < 0.01$.

than those in the healthy people, which confirmed that there was a chronic inflammatory reaction in the peripheral blood of epileptic patients. Clinical trials have demonstrated that patients with epilepsy have different degrees of immune disorders and chronic inflammatory reactions, which also play an important role in the formation of epileptic lesions and recurrent seizures [20–22]. Neurological disorders such as seizures and encephalitis may disrupt the blood-brain barrier (BBB) structure [23]. Cytokines such as IL-1 can act on vascular endothelial cell receptors and destroy tight junctions and basal membranes [7]. In addition, cytokines can also lead to the release of a large number of angiogenic factors, thereby increasing vascular permeability [24]. Pro-inflammatory cytokines disrupt the blood-brain barrier through these possible pathways, thus promoting recurrent seizures. Some scholars have found that in some animal models and patients with temporal lobe epilepsy, due to the destruction of the blood-brain barrier, proteins such as albumin in peripheral blood can cross the blood-brain barrier, and accumulate in microglia and star paper cells [25]. Through the above series of processes, the structure of functional cells is destroyed, leading to neuronal apoptosis, reducing the seizure threshold, and promoting repeated seizures [19]. By destroying the blood-brain barrier and activating glial cells, this inflammation leads to changes in gene expression, loss of neurons, synaptic reorganization and neuronal overexcitation, leading to changes in susceptibility to seizures and a decrease in seizure thresholds [26]. Through the above pathways, pro-inflammatory cytokines can lead to neuron apoptosis, glial cell proliferation, moss fiber germination, resulting in hippocampal atrophy, hippocampal sclerosis and other pathological changes related to epilepsy [7,27]. In an animal study, it was also confirmed that elevated levels of pro-inflammatory cytokines can damage nerve cells and increase seizure frequency [28]. In addition, IL-2 has also been found to promote seizures in various epileptic mouse models [28]. The above studies have shown that inflammation may be one of the pathogeneses of seizures.

In this study, by comparing cytokines in peripheral blood between VPA group and LTG group, it was found that the difference valule of IL-1β、IL-6 and TNF-α before and after treatment in LTG group significantly higher than that in VPA group, which suggested that lamotrigine may inhibitie the secretion of proinflammatory cytokines in the peripheral blood of patients with epilepsy. The results of Eman Y confirmed that LTG can inhibit the secretion of pro-inflammatory cytokines in a mouse LPS/conA-induced inflammation model [29]. Some scholars through an in vitro experiment found that lamotrigine can not only inhibit the secretion of cytokines in

mice, but also inhibit the secretion of cytokines in pm and RAW264.7 cells [30]. EMAN Y. ABU-RISH et al. also observed the effects of lamotrigine on spleen cell proliferation and cytokine secretion induced by cona in vitro, suggesting that lamotrigine significantly inhibited spleen cell proliferation, thus inhibiting splenocyte secretion of cytokines such as IL-2 and TNF- α^9. The above experiments provide clear evidence for the anti-inflammatory effects of LTG in an inflammatory mouse model and may contribute to our current understanding of how LTG plays a role in immune and inflammatory processes in epileptic patients. LTG has also been shown in clinical trials to inhibit the secretion of proinflammatory cytokines such as IL-2, IL-1β, and TNF-α in the peripheral blood of healthy individuals [8]. We try to explore the pharmacological mechanism of LTG regulating cytokine secretion. One possible explanation for how LTG affects cytokines might be through the regulation of ion channels. Lamotrigine is a sodium channel blocker that inhibits voltage-sensitive sodium channels in neurons. By inhibiting the ion channels expressed by immune cells such as B cells, T cells and macrophages, to regulate the key functions of these cells, including cytokine secretion, differentiation, cytotoxicity and phagocytosis, thereby inhibiting the release of proinflammatory cytokines [31,32]. The GABA system may be another possible mechanism by which LTG affects the level of cytokines in the peripheral blood of patients with epilepsy. In recent years, GABA has been shown to be a molecule with immunomodulatory effects, which can regulate a variety of cell functions, including cell proliferation, cytokine secretion, phagocytic activity and chemotaxis [33]. LTG can inhibit the production of cytokines by acting on GABA system, so as to achieve anti-inflammatory effect [34]. Other animal experiments have proved that LTG significantly reduces the level of TNF- α in rats through the mechanism of GABA [35]. Studies have shown that lamotrigine can relieve mood disorders in patients with elevated cortisol levels by reducing glutamate release and blocking the effects of stress or corticosteroids on the hippocampus [36]. Corticosteroids are known to inhibit the inflammatory response [37], and we hypothesized that lamotrigine might affect cytokine levels through the corticosteroid pathway. Timo Jendrik Faust Mann et al. found that the activity of microglia and astrocytes decreased significantly after LTG treatment in inflammatory model mice, and it is well known that the activation of microglia and astrocytes can lead to high expression of proinflammatory cytokines, suggesting that LTG may inhibit the production of cytokines by inhibiting the above-mentioned cells [38]. Pro-inflammatory cytokines can cause a breakdown of the blood-brain barrier, enter the brain, activate glial cells, and lead to inflammatory storm, which leads to the increase of peripheral blood cytokine levels. There is evidence that LTG can repair the blood-brain barrier damage caused by central nervous system diseases, thus interrupting this positive feedback pathway and reducing the level of cytokines [39].

Among the many comorbidities of epilepsy, the incidence of depressive syndrome is among the top [40], and recurrent seizures can lead to depression. Stigma and rejection from peers, social discrimination, self-denial and side effects of treatment may be important causes of depression. Epilepsy combined with depression seriously affects the quality of life of patients and further worsens the outcome of epilepsy. Lamotrigine, as a mood stabilizer, has been proven to be effective in relieving depression in patients with epilepsy and has been widely used in clinical practice in epileptic patients with depression [41]. By comparing the scores of the depression scale of the VPA group and the LTG group, it was found that the difference valule of SDS and HAMD before and after treatment in LTG group significantly higher than that in VPA group. Further correlation analysis of IL-1β, IL-6, TNF-α and depression scale in the LTG group indicated that IL-1β, TNF-α and SDS score were significantly positively correlated, and TNF-α was positively correlated with HAMD scores. The difference values of the above indices were included in multiple linear stepwise regression analysis, suggesting that TNF-α was closely related to depression in epileptic patients, with the increase of TNF-α level, the degree of depression in epilepsy patients became more serious. This study suggests that inflammatory cytokines may be involved in the occurrence and development of depression. Some scholars have proposed the "cytokine hypothesis of depression", suggesting that Cytokines affect depressive behavior by regulating neuroendocrine, neurochemical and other pathways [42]. Himmerich measured the levels of TNF-α, soluble TNF receptor (sTNF-R) p55 and sTNF-R p75 in the peripheral blood of 568 subjects and 62 patients with acute depression and found that the levels of sTNF-R p55, sTNF-R p75 and TNF-α in patients with acute depression were significantly higher than those in the general population [43]. The above experimental results provide support and evidence for the important role of TNF-α system in the occurrence and development of depressive syndrome. Serotonin deficiency may plays a key role in the pathogenesis of depression. Bourin et al. also suggested that LTG may play an antidepressant role by modulating the serotonin system [44]. Serotonin deficiency is obvious in patients with depression, and serotonin reuptake inhibitors can lead to inactivation of serotonin transporter, thus improving depressive symptoms [45]. In fact, Zhu et al. found that TNF-a can enhance serotonin reuptake by stimulating rat embryonic raphe cell lines [46]. The production of a large number of pro-inflammatory cytokines such as TNF- α activates tryptophan and 5-hydroxytryptamine degradation enzyme indoleamine-2-dioxygenase (IDO), the activation of IDO can lead to the increase of serotonin consumption and the production of glutamatergic agonists [47]. More and more studies have also proposed that the increase of glutamatergic nerve transmission plays a key role in the pathogenesis of depression [47]. These results all confirmed that TNF-a and other proinflammatory cytokines may be important in the pathogenesis of epilepsy complicated by depression. Perhaps it can be used as a biomarker for early screening of epilepsy complicated with depressive mood and provide a possible target for treatment and intervention of depression.

The limitation of this study is that the subjects received different doses of lamotrigine and sodium valproate, and the effect of seizure control itself on cytokines and depression cannot be completely ruled out. More animal experiments and clinical studies are needed to further explore and confirm. In addition, due to the small sample size of this study, the lack of data on other antiepileptic drug groups, and the selected subjects were a selected group of epileptic patients, which may increase the possibility of false positive results. In the future, we will expand the sample size and compare a variety of different antiepileptic drugs to improve the credibility of the study.

5. Conclusion

In conclusion, this study shows that there is a certain correlation between the level of pro-inflammatory cytokines and depression in

epileptic patients. Lamotrigine can inhibit the secretion of proinflammatory cytokines in peripheral blood of patients with epilepsy, lamotrigine improves depression in patients with epilepsy, which may be related to the reduction of TNF-α level. This may be the pharmacological mechanism of its mood-stabilizing effect.

Declarations

Ethics approval Ethical approval for this study was obtained from the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2021-KL281-01).

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Ethical standard

Informed consent and permission to publish her information were obtained from the patient.

CRediT authorship contribution statement

Xin Du: Conceptualization, Data curation, Methodology, Writing – original draft. **Bingbing Wang:** Data curation, Investigation. **Heng Wang:** Formal analysis, Investigation. **Qingyun Li:** Investigation, Methodology, Software. **Xinyu Li:** Methodology. **Peng Hu:** Data curation. **Qingwei Lai:** Data curation, Formal analysis. **Hongbin Fan:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33129.

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