

Effects of Cerebrospinal Fluid AMPA Receptor Levels on the Clinical Efficacy of Lamotrigine in the Treatment of Epilepsy

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Abstract

Abstract Background Epilepsy is one of great health burden in the world, deeply effects epilepsy population's mental and physical health,some can totally recover through effective treatment, while some others are difficult to recover even have life risks when seizure attacks. In that case,we explore the effects of cerebrospinal fluid AMPA receptor levels on the clinical efficacy of lamotrigine in the treatment of epilepsy.We believe our work might have an implication in the treatment of epilepsy. **Methods** The 70 cases of epilepsy in our hospital were diagnosed and selected in this study from December 2016 to October 2018; The AMPA receptor content of patients in cerebrospinal fluid were determined by enzyme linked immunosorbent assay; The patients were paired into high AMPA group (n=34) and low AMPA group (n=36) according to the median value at 4.08 ng/ml. Clinical efficacy and the incidence of adverse reactions were compared between two groups. **Results** Before treatment, there was no significant difference in seizure frequency between the two groups ($P>0.05$); After treatment for 6 months and 12 months, the seizure frequencies of the two groups were gradually reduced ($P<0.05$); Moreover, the number of seizures in the low AMPA group were significantly less than those in the high AMPA group ($P<0.05$); The response rate of high AMPA group was 79.41%, which was significantly lower than that in the low group AMPA ($\chi^2=6.055$, $P=0.048$); The improvement on the efficiency of electroencephalogram in the high AMPA group was 67.65%, which was significantly lower than that in the low AMPA group ($\chi^2=4.686$, $P=0.030$); However, there was no significant on the incidence of adverse reactions between two groups ($\chi^2=0.202$, $P=0.653$). **Conclusions** AMPA receptor plays an important role in the development of epilepsy and the low AMPA receptor level patients were more efficacies to the treatment of lamotrigine. **Keywords** Lamotrigine; Epilepsy; AMPA receptor.

Background

Epilepsy is a disorder characterized by chronic and recurrent transient brain dysfunction syndrome, is a relative common neurological disorder worldwide ,a systematic analysis showed that there is approximately 45.9 million epilepsy patients around global, and the year of 2016 age-standardised rates increased 5.6 % compared with 1990, the incidence rates is around 25/1000 capita—which is follow to the incidence rates of stroke^[1]. Although there are increasing option treatments for epilepsy,pharmacological treatment still remains the first choice to control epilepsy. Lamotrigine(LTG) belongs to Benzotriazine derivatives,is a novel broad -spectrum antiepileptic drugs (AEDs) widely used in the treatment of partial and generalized seizures as monotherapy^[2], also can be an add-on therapy among children above 2 years and adults epilepsy with positive clinical tolerability.Lamotrigine is widely used in epilepsy population since it's efficacy and safety have been profoundly approved after many years'clinical observation. Currently,although some Chinese researchers have devoted themselves into the improvement of epilepsy treatment options, there are rare reports about studies on mechanisms between neurotransmission receptors and AEDs .The alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid(AMPA) receptor are the one of major mediators of glutamate-mediated excitatory neurotransmission , hyperactivation of AMPA receptor can provoked many acute neurologic function injury which could be the underlying

mechanism of seizure onset^[3, 4]. Hence, we recruited 70 epilepsy patients who seek medical treatment in our hospital, study the effects of cerebrospinal fluid AMPA receptor levels on the clinical efficacy of Lamotrigine in the treatment of epilepsy, and provide clinical evidence to improve epilepsy's treatment.

Methods

1 Materials

We recruited 70 epilepsy patients in the encephalopathy department of the first affiliated hospital of Guangxi university of Chinese medicine during December 2016 to October 2018, which includes 42 male cases and 28 female cases, age are between 18 years old to 63 years old, average age (42.19 ± 12.80) years old, disease course between half year to 12 years, average disease course (5.29 ± 2.42) years . We classified these patients into generalized-onset (46 cases) and partial-onset (24 cases) according the International League Against Epilepsy (ILAE) classification^[5]. All the recruited patients accordant to the following criteria: ① Completeness of the initial accurate diagnosis of epilepsy base on clinical manifestation, regular electroencephalogram (EEG) and/or video EEG; ② Naïve to other AEDs before treatment or intolerability AEDs due to high adverse effects ; ③ No apparent impairment of heart, lung, hepatic and renal organs, absence of other serious disease , progressive nervous system disease and mental disease; ④ No history of alcohol dependence and drug abuse; ⑤ No contraindications with the use of Lamotrigine or no take any other medicines which can affect lamotrigine's efficacy at the same time. ⑥ Females not in pregnancy and lactation. This study was approved by the Ethics Committees of the First Affiliated Hospital of Guangxi University of Chinese Medicine , all the patients and family provided informed consent to participant.

2. Interventions

Lamotrigine (trade name: Lamictal, purchased from GlaxoSmithKline, Tianjin, SFDA approval number: J20130026 ① 50 mg per table). The initial dosage is prescribed at 12.5 mg daily, then uptitrated to dosage of 25 mg in ten days, twice a day; During experiment, dose adjustment was according to the seizure frequency, increment dosage of 12.5 mg every ten days until reach dosage of 100 mg to 200 mg, twice a day ; The dosage was maintained once they reach the maximal efficacy . The treatment course lasts 12 months. Patients were tested blood routine , urine routine, hepatorenal function and immunity indication every 3 months. Patients were observed closely whether they had severe adverse effects such as allergic rash.

3. Evaluation of Clinical Efficacy

Generally, we depend on no seizure occur within one year to evaluate the efficacy of Lamotrigine^[6]. In another perspective, we can also apply the EEG to help us evaluate the efficacy, base on the *clinical criteria of electroencephalography*^[7], the EEG is classified into: normal EEG of level first; mild abnormal EEG of level second ; moderate abnormal EEG of level third; severe abnormal EEG of level fourth. Classification of mild, moderate, and severe abnormal EEG are subject to abnormal EEG. If the EEG has

been improved after treatment then it was regarded as effective, otherwise it was regarded as not effective.

4.Measurement of CSF AMPA receptor content

The CSF was collected by technique of lumbar puncture, and was centrifuged for 10 min at 2,000 rpm immediately after its collection and the supernatant was stored at a refrigerator in temperature below 80°C in order to avoid repeat freeze thawing. The expression level of CSF AMPA receptor were measured by enzyme linked immunosorbent assay (ELISA)according to the manufacturers' instructions by laboratory technology employees , the kit was purchased from Shanghai Chaoyan Biotechnology Company Limited (article No.SEE803Hu).

5.Statistical analysis

We performed data analyses with SPSS (version 19.0), quantitative data analyses with mean \pm standard deviation. Comparative between two groups analysis with independent sample of Student-t test. Comparative between multi-group analyses with one-way analysis of variance. Numeration data analyses with constituent ratio, comparative between two groups analyses with Chi-squared (χ^2)test,size of test ($\alpha=0.05$).

Results

1.Outcome of Measurement of CSF AMPA Receptor content

The mean level of all patients AMPA receptor is 6.19 ± 2.21 ng/mL; According to the medium value of 4.08 ng/mL, patients were divided into high AMPA group (34 cases, the level of AMPA >4.08 ng/mL) and low AMPA group (36 cases, the level of AMPA ≤ 4.08 ng/mL).

2.Basic information comparative between high AMPA group and low AMPA group

Difference between two groups patient's age, gender, prodrome, seizure type, intracranial pressure,etc have no statistically significant ($P>0.05$)(Table 1)

3.Level of CSF AMPA receptor content impact on lamotrigine clinical efficacy

The rate of high AMPA group patient no seizure recur is 79.41% $\left[27/34\right]$ within one year, which is apparently lower than low AMPA group 97.22% $\left[35/36\right]$.The difference have statistical significance. $\chi^2=6.055, P=0.048$)(Table 2).

4.Impact of CSF AMPA receptor concent on lamotrigine's treatment reflect on EEG

Rate of abnormal EEG between high and low AMPA group have no statistical difference before treatment $\chi^2=0.005, P=0.942$.However, rate of abnormal EEG on low AMPA group is 63.89% after treatment,

apparently lower than high AMPA group(85.29%), the difference have statistical significance $\chi^2=4.194$, $P=0.041$ (Table 3)

5.Effects of CSF AMPA receptor content on lamotrigine 's adverse effects

There was 9 cases happened adverse effects after treatment with lamotrigine , 5 cases in high AMPA(rate is 14.71%,5/34) and 4 cases in low AMPA(rate is 11.11%,4/36), difference have no statistical significance $\chi^2=0.202$, $P=0.653$).

Discussion

Glutamate receptor is a majority of excitatory neurotransmission receptor in the central nervous system among mammalian, it divided into ionotropic and metabotropic^[8].Specifically,ionotropic glutamate contains N-methyl-D-aspartate (NMDA) AMPA receptor and kainite (KA) receptor, all of them are the main mediators in the brain function,such as synaptic transmission, long-term synaptic potentiation, synaptic plasticity and learning- memorizing and so on ^[9].Previously studies have showed that AMPA receptor also belongs to chemical voltage-gate channel receptors. Activation of AMPA receptor can initiate the opening of ion channel immediately, excessive the influx of monovalent cation $\text{Na}^+ \text{K}^+$ and cause depolarization of postsynaptic membrane^[10].At the same time ,activation of AMPA receptor can also leads the influx of extracellular Ca^{2+} that trigger a cascade events of biochemical response which can change the characteristic of membrane and excessive the generation of long-term potentiation.In the research of pathology mechanism on epilepsy, researchers have discovered that AMPA receptor channel GluR2 subunit can be replaced by GluR1 subunit and GluR3 subunit, enhanced neuron uptake the Ca^{2+} ,provoked the brain injury in hippocampal area of CA1 and CA3 that trigger seizure frequency^[3].Additionally, injection of AMPA receptors inhibitor before seizure onset can brings a significant impact of neuroprotective function, which can decrease seizure frequency effectively^[11]. All of this studies have fully indicated that AMPA receptor plays an important role in epilepsy's onset and progressive ,treatments target on AMPA receptors might be helpful to control seizure attack,

Lamotrigine is a Benzotriazine derivatives,a current novel broad -spectrum antiepileptic drugs (AEDs),mechanism of lamotrigine on treatment of controlling epilepsy includes the inhibition release of glutamate and aspartic acid, then selectively functions on Na^+ channel and block the binding of excitatory glutamate and it's receptors^[12].Our study rely on patient's CSF AMPA receptor content 's median value to paired into two groups, results have shown that after month 6 and month 12 in treatment of lamotrigine, all patients seizure frequency was gradually decreasing and confirm lamotrigine's value on epilepsy,which was consist with the previous studies^[13, 14]. Most importantly ,our study have also discovered that seizure frequency in low AMPA group apparently lower than high AMPA group, it elucidated that the level of AMPA receptor might have an impact during lamotrigine's treatment in epilepsy.At the same time, through extensive comparative between two group's clinical efficacy, we found that high AMPA group 's response rate and the rate of EEG's improvement were lower than low AMPA

group. It further indicates that the less content of AMPA receptor, the better of clinical efficacy of lamotrigine. We hypothesize that it might contributed to low excitatory glutamate in low AMPA receptor, and lamotrigine selectively inhibit the neuron depolarization and high-frequency discharge in seizure lesions, stabilize neuron Na^+ channel, block the transmission of overexcitation synapse to postsynaptic membrane, then decrease the frequency of seizure and produce a positive clinical efficacy. In addition, the adverse effects between two groups have no significant difference, it suggested that the content of AMPA receptor have no impact on lamotrigine's safety and reliability.

As stated above, our study suggest that CSF AMPA receptor plays a significant role in epilepsy's onset and progressive, and low content of AMPA receptor is better in option of lamotrigine. The limitation of our study is about small case, short duration and no observation in long term. Further high-quality research is needed to fully evaluate the efficacy of CSF AMPA receptor effect on lamotrigine's treatment in epilepsy.

Conclusions

As mentioned above, AMPA receptor plays an important role in the development of epilepsy and the low AMPA receptor level patients were more efficacies to the treatment of lamotrigine.

Abbreviations

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; LTG: lamotrigine; AEDs: antiepileptic drugs; ILAE: International League Against Epilepsy; EEG: electroencephalogram; CSF: cerebrospinal fluid; ELISA: enzyme linked immunosorbent assay; KA: kainite. NMDA: ionotropic glutamate contains N-methyl-D-aspartate.

Declarations

Acknowledgements

Not applicable

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Not applicable

Availability of data and materials

All data will be secured in the hospital computer and will be available on request from the corresponding author.

Authors' contribution

QJT and YHL conceived the idea, designed the study and produced the first draft of the study. YHL helped with the statistical analysis. TLW, JWY, TBW and HHL-all have provided intellectual content in the preparation and editing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The First Affiliated Hospital of Guangxi University of Chinese Medicine's Research Ethics Committee has approved the study and all the participants were provided written informed consent.

Consent for publication

Written informed consent was obtained from the patients for publication of this study and any accompanying data.

Competing interests

Authors declare no financial or non-financial interests.

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Tables

	high AMPA group	Low AMPA group	t/χ^2 vaule	P vaule
Age (year)	40.95±13.06	43.51±11.93	0.857	0.395
Gender (male/female)	19/15	23/13	0.467	0.494
Prodrome			0.508	0.917
Fever	22	23		
Abdominal pain and diarrhea	3	4		
Cold sore	2	1		
No symptoms	7	8		
Seizure type			0.827	0.843
Generalized onset	2	3		
Simple partial onset	1	3		
Complex partial onset	1	3		
Partial secondary generalized onset	30	29		
Intracranial pressure			0.183	0.669
normal	13	12		
abnormal	21	24		

Table 1 Basic characteristic comparative between high AMPA group and low AMPA group

case(n)	no recur within one year	rates of no recur within one year	χ^2 value
PA 34	27	79.41(27/34)	6.055 0.048
PA 36	35	97.22(35/36)	

Table 2.Level of CSF AMPA receptors impact on lamotrigine clinical efficacy

	group	case[n]	0	1	2	3	Rate of abnormal[%]
Before treatment	High AMPA	34	3	14	10	7	91.18[31/34]
	Low AMPA	36	3	13	12	8	91.67[33/36]
	χ^2 value						0.005
	<i>P</i> value						0.942
After treatment	High AMPA	34	5	16	8	5	85.29[29/34]
	Low AMPA	36	13	15	5	3	63.89[23/36]
	χ^2 value						4.194
	<i>P</i> value						0.041

Table 3 Impact of CSF AMPA receptors content on lamotrigine’s treatment reflect on EEG