Risk Factors of Elevated Blood Ammonia Level in Epilepsy Patients Treated With Lamotrigine

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Abstract

Background

The aim of this study was to explore the effect of lamotrigine (LTG) on blood ammonia level in patients with epilepsy and identify risk factors affecting blood ammonia level.

Methods

This study included 91 epilepsy patients who were treated with LTG at Department of Neurology, Zhongshan Hospital, Xiamen University from January 2011 to April 2016, and were followed up for three years. Blood samples were taken during the interictal state and analyzed for blood LTG and ammonia levels.

Results

Total 46.1% of the samples exceeded the median blood ammonia level, and 2.1% of patients had hyperammonemia. Blood ammonia level was positively correlated with LTG blood concentration. LTG combined with valproic acid (VPA) therapy, seizure within one year, and elevated neutrophils affected blood ammonia level.

Conclusion

Blood ammonia level was significantly correlated with plasma concentration of LTG. LTG combined with VPA therapy, seizure within one year, and elevated neutrophils may be risk factors for elevated blood ammonia level in epilepsy patients treated with LTG.

Introduction

Lamotrigine (LTG) is a new type of broad spectrum anti-epileptic drug, which can inhibit the presynaptic release of excitatory neurotransmitters by blocking sodium channels. (1, 2)

LTG is widely used in the clinic to treat various seizures and bipolar depression. (3, 4) Although LTG has the characteristics of high efficacy and low incidence of side effects, the risk of side effects could not be ignored (5). It has been reported that LTG might potentiate valproic acid (VPA) induced hyperammonemic encephalopathy (VHE) (6). A case report showed that one patient developed encephalopathy after LTG treatment and the symptoms improved after reducing the amount of LTG (7).

We hypothesized that the side effect of VHE after LTG therapy in epilepsy patients may be related to blood ammonia level. However, little is known about the effect of LTG on blood ammonia level. Therefore,

this study aimed to explore the effect of LTG on blood ammonia level in patients with epilepsy and identify risk factors affecting blood ammonia level.

Materials And Methods

Subjects

This was a single-center, prospective, observational study approved by the Ethics Committee of Zhongshan Hospital following the Declaration of Helsinki. All patients provided written informed consent and received medical examinations and interviews.

All data were collected from epilepsy patients diagnosed at the Department of Neurology, affiliated Zhongshan hospital, Xiamen University (Xiamen, China) from January 2011 to April 2016. The clinical data of the patients were collected, including age, gender, age of onset, duration of epilepsy, symptoms, etiology, epilepsy control, dose and duration of LTG, medication regimen, blood ammonia level, comorbidities, and biochemical indexes. CT or MRI was examined before medication and EEG was examined before and after medication. EEG was assessed by a specialist neuroelectrophysiologist.

The inclusion criteria were: 1. diagnosis of epilepsy according to the International Antiepileptic Alliance (ILAE);(8) 2. older than 17 years and received LTG monotherapy or combination therapy. Exclusion criteria were: 1. had hyperammonemia due to any cause except for LTG treatment such as liver failure, urea cycle defects; 2. switched to other drugs because of illness; 3. received treatment with other antiepileptic drugs (except VPA); 4. irregular medication or poor compliance; 5. pregnancy; 6. received epilepsy surgery.

Assessment of blood ammonia level

Blood samples were collected in heparinized tubes, and centrifuged at 3,000 rpm for 10 min to obtain plasma samples. The plasma ammonia was analyzed at the Department of Laboratory Medicine, Zhongshan Hospital, Xiamen University. Blood ammonia level > 60 μmol/L in male and >51 μmol/L in female were considered as hyperammonemia. According to the median of blood ammonia level (35 μmol/L), patients were divided into two groups: patients with blood ammonia level >35 μmol/L were grouped as high blood ammonia group, and the remaining patients were grouped as low blood ammonia group.

Assessment of blood LTG level

Plasma level of LTG was measured using ARK Lamotrigine assay (homogeneous enzyme immunoassay) in Siemens Viva-E automatic drug concentration analysis system.

Statistical analysis

Data analysis was performed by using SPSS version 24. Pearson chi-square and Fisher exact tests were used for classified variables. Continuous variables were compared using Mann-Whitney U test. Pearson

correlation was performed to test the association between continuous variables, including plasma levels of LTG and ammonia. P-value < 0.05 was considered statistically significant.

Results

Demographic data of the patients

A total of 91 patients (55 women and 36 men) were included in this study. The demographic data of the patients were listed in Table 1. The median age was 26 (20-33) years. The median body mass index was 21.76 (19.81-23.51) kg/m2. The median duration of epilepsy was 8 (4-13) years. Total 85 (93.4%) patients had partial seizure and 6 (6.6%) patients had generalized seizure. Total 56 patients (61.5%) received LTG monotherapy and 35 patients (38.5%) received LTG and VPA combination therapy. Total 47 (56.0%) patients had temporal lobe epilepsy and 37 (44.0%) patients had non-temporal lobe epilepsy. Total 55 (60.4%) patients had a seizure within one year and 36 (39.6%) patients had no seizure within one year. The dosage of LTG ranged from 25 to 600 mg/day, and blood LTG level ranged from 0.21 to 19.90 μg/mL. Blood ammonia level ranged from 10 to 61 μmol/L.

Table 1
Demographic data of 91 patients receiving LTG therapy

Characteristics	
Age (year)	26(20-33)
Gender: male/female	36/55(39.6% vs 60.4%)
Body mass index (kg/m2)	21.76(19.81-23.51)
Age at onset (year)	17(12-25)
Duration of epilepsy (year)	8(4-13)
Seizure type; N (%)	
Partial	85(93.4%)
Generalized	6(6.6%)
Mode of LTG therapy; N (%)	
LTG monotherapy	56(61.5%)
LTG combined with VPA therapy	35(38.5%)
Blood LTG level (ug/mL)	5.20(2.90-8.16)
Plasma level of ammonia (umol/L)	35(25-41)
Causes of epilepsy	
Temporal lobe epilepsy	47(56.0%)
Nontemporal lobe epilepsy	37(44.0%)
Seizure within one year	
Yes	55(60.4%)
No	36(39.6%)
Dose of LTG use (mg/day)	200(100-200)
Comorbidity; N (%)	
Yes	11(12.1%)
No	80(87.9%)
LTG: lamotrigine, VPA: valproic acid, IQR: interquartile range (25th percentile, 75th percentile). Continuous values were expressed as median (IQR).	

Risk factors of elevated blood ammonia level

The clinical characteristics of patients with or without elevated blood ammonia level were compared. The results showed that significant predictors of elevated blood ammonia level included LTG combination therapy (P=0.036), seizure within a year (P=0.047), blood LTG level (P=0.001), neutrophil (P=0.038) (Table 2). According to Pearson correlation analysis, blood ammonia level was correlated with blood LTG level (r=0.046, P□0.001) (Figure 1).

Table 2
Risk factors of blood ammonia level.

Blood ammonia level			
	Low(N=49)	High(N=42)	P-value
Age (year)	26(19-34)	26(23-32)	0.602
Gender			0.869
male	19	17	
female	30	25	
Body mass index (kg/m^2)	21.97(19.90-23.56)	21.74(19.76-23.47)	0.915
Age at onset (year)	15(9-26)	18(15-25)	0.176
Duration of epilepsy (year)	8(4-14.5)	7(3.75-12)	0.505
Seizure type; N (%)			0.51
Partial	45	40	
Generalized	4	2	
Mode of LTG therapy; N (%)			0.036
LTG monotherapy	35	21	
LTG combined with VPA therapy	14	21	
Blood LTG level (ug/mL)	3.94(2.01-6.22)	6.89(4.68-9.17)	0.001
Causes of epilepsy			0.074
Temporal lobe epilepsy	20	27	
Nontemporal lobe epilepsy	23	14	
Seizure within one year			0.047
Yes	25	30	
No	24	12	
Dose of LTG use (mg/day)	0.20(0.10-0.20)	0.20(0.10-0.20)	0.877
Comorbidity; N (%)			0.552
Yes	44	36	

LTG: lamotrigine, VPA: valproic acid, AST: aspartate transaminase, ALT: alanine aminotransferase, ALK-P: alkaline phosphatase, γGT: gamma glutamyl transpeptidase, eGFR : Estimated Glomerular Filtration Rate, IQR: interquartile range (25th percentile, 75th percentile). Continuous values were expressed as median (IQR).

Blood ammonia level			
No	5	6	
Laboratory data			
Leukocyte(10^9/L)	6.02(5.18-7.57)	6.61(5.45-7.98)	0.402
Neutrophils(10^9/L)	3.22(2.63-4.33)	3.60(3.15-4.53)	0.038
Platelets(10^9/L)	241(210-274)	241(199-272)	0.491
Blood creatinine (umol/L)	60.20(49.75-68.70)	66.20(52.05-71.78)	0.161
AST(U/L)	18.80(14.40-21.90)	19.60(16.93-23.78)	0.222
ALT(U/L)	12.3(8.75-18.35)	15.25(11.00-23.68)	0.074
ALK-P(U/L)	73.8(60.8-96.2)	69.60(58.63-89.53)	0.489
r-GT(U/L)	19.10(14.30-26.15)	24.45(13.98-38.88)	0.076
LTG: lamotrigine, VPA: valproic acid, AST: aspartate transaminase, ALT: alanine aminotransferase, ALK-P: alkaline phosphatase, γGT: gamma glutamyl transpeptidase, eGFR : Estimated Glomerular Filtration Rate, IQR: interquartile range (25th percentile, 75th percentile). Continuous values were expressed as median (IQR).			

Discussion

In this study, based on the analysis of 91 epilepsy patients admitted to a single-center, we found that blood ammonia level was significantly correlated with blood LTG level. In addition, LTG combined with VPA therapy, seizure within one year, and elevated neutrophils increased the risk of elevated blood ammonia level.

The association between blood ammonia level and anti-epileptic drugs has been investigated. (9–11) The most important finding of our study is that LTG was closely related to elevated blood ammonia level, contrary to previous studies. (10, 12) This may be caused by different definitions of elevated blood ammonia level. In this study, only 2 (2.1%) patients developed hyperammonemia, and they were asymptomatic.

We found that the combined use of LTG with VPA increased the risk of VHE, consistent with previous study (6). This may be related to the competition between LTG and VPA for UDP-glucuronosyltransferase (UGT) metabolic pathway. When LTG is used in combination with VPA, it will increase the concentration of LTG (13, 14). However, one study showed that the combination of VPA and LTG did not cause an increase in blood ammonia level (10), while another study showed that LTG significantly reduced the risk of hyperammonemia in patients using VPA (12). The contradiction can be explained by different definitions of elevated blood ammonia level.

Seizure within one year will increase the risk of elevated blood ammonia level. Consistent with our results, previous studies reported that transient hyperammonemia could be an indicator of a recent epileptic seizure. (15, 16) Upon epileptic seizure, muscle contraction will lead to elevated blood ammonia level. (17) This may also be related to the adjustment of anti-epileptic drugs after a seizure. Elevated neutrophils are usually related to inflammation, and inflammation may lead to increased blood ammonia level. (18, 19)

This study has several limitations. The main limitation is that we grouped the patients according to the median blood ammonia level. In the relatively high blood ammonia group, the patient's blood ammonia level may be normal. Second, sample size of hyperammonemia was very small, and we are not sure whether LTG treatment will cause hyperammonemia.

In conclusion, the use of LTG in adult patients with epilepsy was positively correlated with blood ammonia level. LTG combined with VPA therapy, seizure within one year, and elevated neutrophils may be risk factors for elevated blood ammonia level in epilepsy patients with LTG therapy.

Declarations

Ethics approval and consent to participate：This is study approved by the Ethics Committee of Zhongshan Hospital in accordance with the Declaration of Helsinki. All patients provided written informed consent and received medical examinations and interviews.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Y. C and J.C, and X.Z wrote the main manuscript text; X.C, and J.Z Completed data collection. R. W prepared figures 1-2. J.M is responsible for the overall plan of the research. All authors reviewed the manuscript.

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Figures

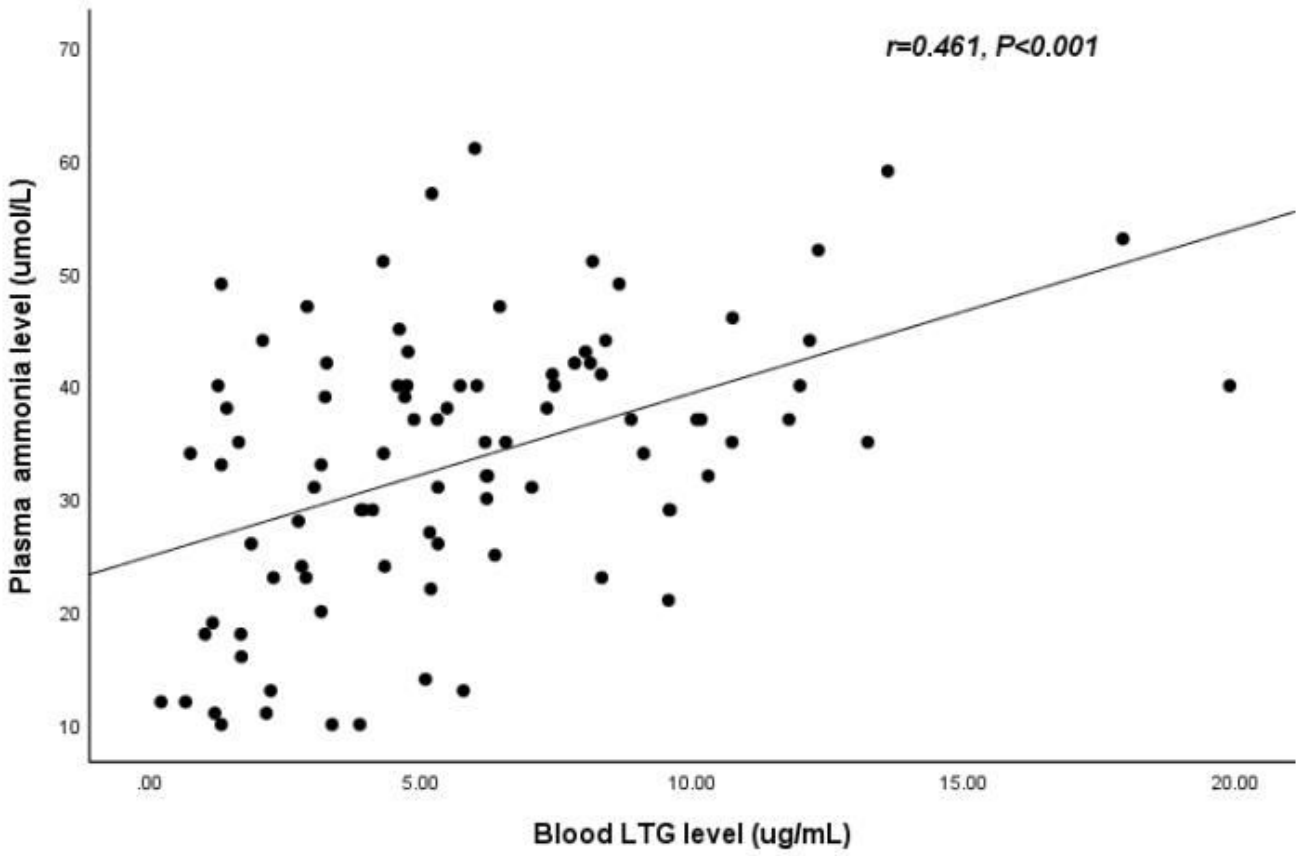

Figure 1

Positive correlation between blood ammonia level and blood LTG level in 91 patients with epilepsy.