

Risk factors of elevated blood ammonia level in epilepsy patients treated with lamotrigine

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Abstract

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.

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 3 years. Blood samples were taken during the interictal state and analyzed for blood LTG and ammonia levels. Total of 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 therapy, seizure within 1 year, and elevated neutrophils affected blood ammonia level. Blood ammonia level was significantly correlated with plasma concentration of LTG. LTG combined with valproic acid therapy, seizure within 1 year, and elevated neutrophils may be risk factors for elevated blood ammonia level in epilepsy patients treated with LTG.

Abbreviations: LTG = lamotrigine, VHE = valproic acid induced hyperammonemic encephalopathy, VPA = valproic acid.

Keywords: blood ammonia, epilepsy, lamotrigine, risk factor

1. Introduction

Lamotrigine (LTG) is a new type of broad-spectrum antiepileptic 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 1 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.

2. Materials and Methods

2.1. 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. Computed tomography or magnetic resonance imaging was examined before medication, and electroencephalogram was examined before and after medication. Electroencephalogram was assessed by a specialist neuroelectrophysiologist.

The inclusion criteria were

1. Diagnosis of epilepsy according to the International Antiepileptic Alliance.^[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).

YC, JC, and XZ contributed equally to this work.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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The authors have no conflicts of interest to disclose.

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4. Irregular medication or poor compliance.
5. Pregnancy.
6. Received epilepsy surgery.

2.2. Assessment of Blood Ammonia Level

Blood samples were collected in heparinized tubes and centrifuged at 3000 rpm for 10 minutes to obtain plasma samples. The plasma ammonia was analyzed at the Department of Laboratory Medicine, Zhongshan Hospital, Xiamen University. Blood ammonia level $>60 \mu\text{mol/L}$ in males and $>51 \mu\text{mol/L}$ in females were considered as hyperammonemia. According to the median of blood ammonia level ($35 \mu\text{mol/L}$), patients were divided into 2 groups: patients with blood ammonia level $>35 \mu\text{mol/L}$ were grouped in as high blood ammonia group, and the remaining patients were grouped in as low blood ammonia group.

2.3. 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.

2.4. 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.

3. Results

3.1. 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 $21.76 (19.81–23.51) \text{ kg/m}^2$. 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. A total of 56 patients (61.5%) received LTG monotherapy, and 35 patients (38.5%) received LTG and VPA combination therapy. A total of 47 (56.0%) patients had temporal lobe epilepsy, and 37 (44.0%) patients had nontemporal lobe epilepsy. A total of 55 (60.4%) patients had a seizure within 1 year, and 36 (39.6%) patients had no seizure within 1 year. The dosage of LTG ranged from 25 to 600 mg/day, and blood LTG level ranged from 0.21 to $19.90 \mu\text{g/mL}$. Blood ammonia level ranged from 10 to $61 \mu\text{mol/L}$.

3.2. 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 ($P = 0.001$), and neutrophil ($P = 0.038$) (Table 2). According to Pearson correlation analysis, blood ammonia level was correlated with blood LTG level ($r = 0.046$, $P < 0.001$) (Fig. 1).

4. Discussion

In this study, based on the analysis of 91 epilepsy patients admitted to a single center, we found that blood ammonia

Table 1
Demographic data of 91 patients receiving LTG therapy.

Characteristics	
Age (y)	26 (20–33)
Gender: male/female	36/55 (39.6% vs 60.4%)
Body mass index (kg/m^2)	21.76 (19.81–23.51)
Age at onset (y)	17 (12–25)
Duration of epilepsy (y)	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 ($\mu\text{g/mL}$)	5.20 (2.90–8.16)
Plasma level of ammonia ($\mu\text{mol/L}$)	35 (25–41)
Causes of epilepsy	
Temporal lobe epilepsy	47 (56.0%)
Nontemporal lobe epilepsy	37 (44.0%)
Seizure within 1 y	
Yes	55 (60.4%)
No	36 (39.6%)
Dose of LTG use (mg/d)	200 (100–200)
Comorbidity, n (%)	
Yes	11 (12.1%)
No	80 (87.9%)

IQR: 25th percentile, 75th percentile. Continuous values were expressed as median (IQR).
IQR = interquartile range, LTG = lamotrigine, VPA = valproic acid.

level was significantly correlated with blood LTG level. In addition, LTG combined with VPA therapy, seizure within 1 year, and elevated neutrophils increased the risk of elevated blood ammonia level.

The association between blood ammonia level and antiepileptic 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 metabolic pathway. When LTG is used in combination with VPA, VPA increases the concentration of LTG.^[13,14] When LTG is used in combination with other antiseizure medications, VPA increases the risk of hyperammonemia through inhibiting carbamyl phosphate synthetase I, which is the key enzyme of ornithine cycle.^[15] The combination of VPA and cannabidiol has been associated with increased risk of hepatic toxicity in patients with Dravet syndrome and Lennox-Gastaut syndrome.^[16,17] However, we found no increase in transaminase in this study. Interestingly, one study showed that the combination of VPA and LTG did not cause an increase in blood ammonia level,^[10] whereas 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 1 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.^[18,19] Upon epileptic seizure, muscle contraction will lead to elevated blood ammonia level.^[20] This may also be related to the adjustment of antiepileptic drugs after a seizure. Elevated neutrophils are usually related to inflammation, and inflammation may lead to increased blood ammonia level.^[21–24]

This study has several limitations. The main limitation is that we grouped the patients according to the median blood

Table 2
Risk factors of blood ammonia level.

Blood ammonia level	Low (n = 49)	High (n = 42)	P value
Age (y)	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 (y)	15 (9–26)	18 (15–25)	0.176
Duration of epilepsy (y)	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 (µg/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 1 y			0.047
Yes	25	30	
No	24	12	
Dose of LTG use (mg/d)	0.20 (0.10–0.20)	0.20 (0.10–0.20)	0.877
Comorbidity, n (%)			0.552
Yes	44	36	
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 (µmol/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
γ-GT (U/L)	19.10 (14.30–26.15)	24.45 (13.98–38.88)	0.076

IQR: 25th percentile, 75th percentile. Continuous values were expressed as median (IQR).

γGT = gamma glutamyl transpeptidase, ALK-P = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate transaminase, IQR = interquartile range, LTG = lamotrigine, VPA = valproic acid.

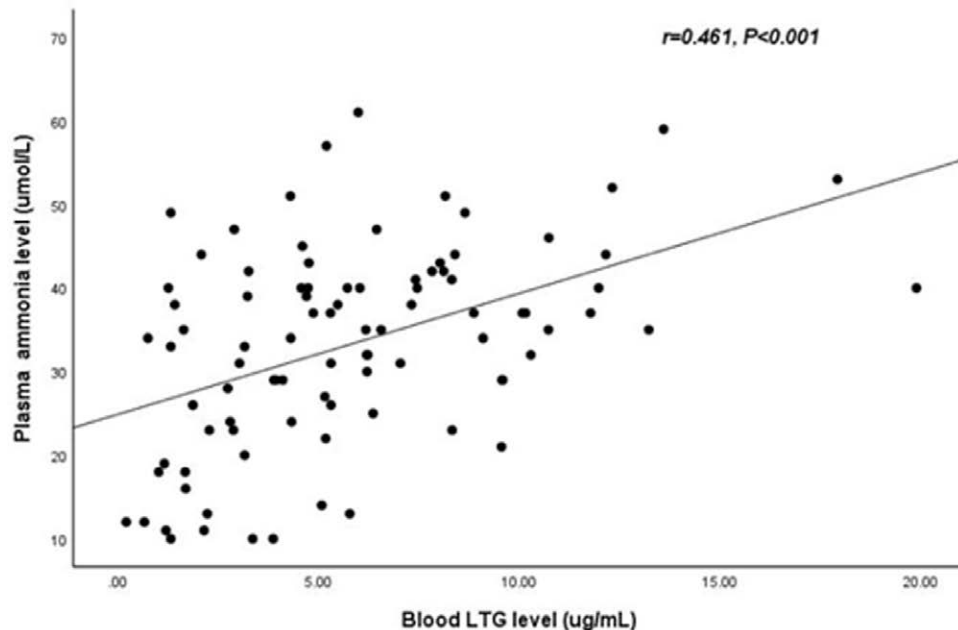


Figure 1. Positive correlation between blood ammonia level and blood LTG level in 91 patients with epilepsy. LTG = lamotrigine.

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 1 year, and elevated neutrophils may be risk factors for elevated blood ammonia level in epilepsy patients with LTG therapy.

Author contributions

Yiqian Chen, Jingzhen Chen, Jiayin Miao and Xiaorong Zhuang conceived the idea of the study; Xingyu Chen and Jianqi Zeng analysed the data; Ru Wang and Jiayin Miao interpreted the results; Yiqian Chen wrote the paper; all authors discussed the results and revised the manuscript.

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