Epilepsy Research 124 (2016) 12–15

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Levetiracetam-induced cutaneous adverse drug reactions were not associated with HLA genes in a small sample of Chinese patients with epilepsy

Fa-Yun Hu [1], Wei Wang [1], Jie-Chuan Ren, Dong-Mei An, Jia-Ni Chen, Dong Zhou *

Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

ARTICLE INFO

Article history:
Received 4 May 2015
Received in revised form 10 April 2016
Accepted 30 April 2016
Available online 2 May 2016

Keywords:
Epilepsy
Levetiracetam
Cutaneous adverse drug reactions
Rash
Human leukocyte antigen

ABSTRACT

Purpose: This study aimed to evaluate the clinical characteristics of levetiracetam (LEV)-induced cutaneous adverse drug reactions (cADRs) and to explore its possible genetic association with the human leukocyte antigen (HLA) genes.
Methods: Nine cases with LEV-induced cADRs were recruited. Demographic and clinical information of these cases was summarized. Additionally, cases were matched with LEV-tolerant controls (1:4). High-resolution *HLA* class I and class II genotyping was performed for each participant. The allele frequencies between the cases and controls were compared.
Results: All LEV-induced cADRs were mild skin rashes which occurred within 28 days of LEV exposure. The mean latency from LEV exposure to skin rash was (15.67 ± 5.41) days (ranging 6–27). The carrier rates of the two alleles, HLA-DRB1*0405 and HLA-DQB1*0401, were higher in cases compared with controls (the same $P = 0.036$, OR = 13.875, 95% CI: 1.273-151.230). The association between the HLA-C*0304 allele and LEV-induced cADRs was boundary ($P = 0.05$, OR = 5.2, 95% CI: 1.086-24.897). However, the above-mentioned HLA alleles didn't reach statistical significance after multiple comparisons.
Conclusions: Safety monitoring was necessary within four weeks after the initiation of LEV treatment, although it has been regarded as a safe antiepileptic drug. Our study failed to show any potential link between HLA alleles and LEV-induced cADRs in Han Chinese. Further studies are needed to clarify the genetic and immunological mechanisms of LEV-induced cADRs.

1. Introduction

Levetiracetam (LEV) was first approved by United States Food and Drug Administration (US FDA) in December 1999 and proved to be effective in both partial and generalized epilepsy syndromes either as adjunctive treatment or monotherapy (Berkovic et al., 2007; French and Pedley, 2008). Unlike other antiepileptic drugs (AEDs), LEV has unique structural feature, novel antiepileptic mechanism and also fewer adverse side effects. One of the most common adverse reactions, AEDs-induced cutaneous adverse drug reactions (cADRs), has been less reported in LEV. To the best of our knowledge, only some scattered case reports of LEV-induced cADRs can be retrieved. The clinical characteristics and genetic mechanisms of LEV-induced cADRs have been unclear.

Recent advances in pharmacogenomics of AEDs may bring us some inspirations. Accumulated evidence confirmed the closely association between some AEDs-induced cADRs and the human leukocyte antigen (HLA) genes. Several important biological markers, including HLA-B*1502 allele (Chung et al., 2004) and HLA-A*3101 allele (McCormack et al., 2011), have been found to have outstanding predictive value for specific AEDs-induced cADRs in different populations. In the present study, we investigated the clinical features of nine epilepsy patients who experienced LEV-induced cADRs and exploratorily examine the possible association of the *HLA* genes with the risk of LEV-induced cADRs in Chinese Han populations.

2. Patients and methods

2.1. Patients

Nine cases with LEV-induced cADRs from epilepsy center of West China Hospital (8 from outpatient clinic and 1 from the ward)

* Corresponding author at: Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan Province 610041, China.
E-mail address: zhoudong66@yahoo.de (D. Zhou).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.eplepsyres.2016.04.008
0920-1211/

Table 1
Demographic and clinical features of the nine case patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Gender	Female	Male	Female	Male	Male	Male	Male	Male	Female
Age (years)	8	31	9	6	51	15	35	64	13
Ethnicity	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese	Han Chinese
History of epilepsy	30 days	2 years	3 years	10 months	1.5 years	3 months	7 months	13 days	15 months
MRI	Normal	Normal	Abnormal	Normal	Normal	Normal	Normal	Abnormal	Normal
EEG	Normal	Abnormal	Abnormal	Normal	Normal	Normal	Normal	Abnormal	Normal
AEDs when rash occurred	LEV	CBZ + LEV	LTG + LEV	LEV	CBZ + LEV	LEV	VPA + LEV	LEV	LTG + LEV
Causative drugs of rash	LEV	LEV	LEV	LEV	LEV	LEV	LEV	LEV	LEV
Dosage of LEV (mg/d)	500	1000	500	1000	750	1000	1000	1000	500
Latency to skin rash	11	15	8	27	23	19	14	6	18
Types of skin rash	MPE	MPE	MPE	MPE	MPE	MPE	MPE	MPE	MPE
Clinical prognosis of rash	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

AEDs: antiepileptic drugs; LEV: levetiracetam; CBZ: carbamazepine; LTG: lamotrigine; VPA: valproate; MPE: maculopapular exanthema.

were included between September 2011 and December 2014. The diagnostic criteria for the patient group were: subjects who developed LEV-induced maculopapular exanthema (MPE) after taking LEV for less than eight weeks. Patients who developed MPE after simultaneously use of other suspicious drugs were excluded. Other common causes of cADRs including over-the-counter drugs, allopurinol, NSAID, antibiotics, HIV and easily allergic foods were also excluded by an experienced dermatologist. MPE is defined as cutaneous itchy and erythematous macules and papules after administration of LEV, and spontaneously resolve within 1-2 weeks after withdrawing the causative drugs (Roujeau and Stern, 1994). Detailed medical records of these patients were retrospectively reviewed and clinical data was shown in Table 1.

2.2. Controls

A group of 36 Han Chinese epilepsy patients who had received or have been receiving LEV treatment for at least 3 months without any adverse drug reactions were recruited as LEV-tolerant controls. The control group was matched for age, gender, ethnicity and LEV dosage.

2.3. HLA genotyping

Written informed consent was obtained from all participants. Genomic DNA of each subject was extracted from peripheral blood lymphocytes according to the standard kit procedures. High-resolution four-digit allele genotyping of the *HLA* class I and class II genes, including HLA-A, -B, -C, -DRB1 and -DQB1, was performed using our previous mature methods (An et al., 2010).

2.4. Statistical analysis

Statistical analyses were performed using SPSS 18.0 software package. The frequency difference of each *HLA* allele between LEV-induced cADRs group and LEV-tolerant control group was separately analyzed by Fisher's exact test. Bonferroni correction was applied to adjust for multiple comparisons. In order to reduce bias in estimating odds ratios (ORs), when zero cell counts were included, ORs were calculated using Haldane's modification, which adds 0.5 to all cells to accommodate possible zero counts (Haldane, 1956). A two-tailed P value of <0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

Nine epileptic patients (6 male, 3 female) with LEV-induced cADRs and 36 LEV-tolerant controls were included. LEV was taken as monotherapy for epilepsy in four patients while as adjunctive treatment in the rest. All of the skin rashes were confirmed as MPE. Routine laboratory examination and temperature were normal. Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), were not observed. All nine patients had the rashes occurred within 4 weeks of LEV exposure. The mean latency from LEV exposure to skin rash was (15.67 ± 5.41) days (ranging 6–27). The average dosage of LEV was (805.5 ± 216.1) mg/day (ranging 500–1000) when the rashes appeared. All skin rashes spontaneously recovered within one week after the withdrawal of LEV, which is considered causative.

3.2. The HLA alleles

All participants were successfully genotyped. The results of *HLA* genotyping for the 9 cases with LEV-induced cADRs were shown in Table 2. Allele frequencies of the *HLA* genes in the two groups were shown in Table 3. Two HLA-DRB1*0405 carriers and two HLA-DQB1*0401 carriers were detected in the 9 patients, respectively. However, we failed to find the two alleles in the controls, suggesting that the two alleles had higher frequencies in patients with LEV-induced cADRs when compared with the LEV-tolerant controls (the same $P = 0.036$, OR = 13.875, 95% CI: 1.273-151.230). The HLA-C*0304 allele also had an increased frequency in LEV-induced cADRs group than that in LEV-tolerant controls, with only a marginal statistical significance ($P = 0.05$, OR = 5.2, 95% CI: 1.086–24.897). However, the above-mentioned HLA alleles did not reach statistical significance after multiple comparisons. The frequency differences of other *HLA* alleles between the two groups did not reach statistical significance ($P > 0.05$).

4. Discussion

LEV, a new generation antiepileptic drug, with novel anticonvulsive mechanism (Hovinga, 2001), is structurally similar to piracetam which is one of the most common nootropic drugs, but different from other currently marketed AEDs. LEV is characterized with insignificant drug interactions and favorable tolerability and safety profile (Lo et al., 2011; Lyseng-Williamson, 2011). The reported adverse effects profile of LEV include somnolence, headache, asthenia, fatigue, dizziness, behavioural disturbances, cutaneous adverse reactions, pharyngitis, infection, abdominal pain, stomach discomfort, insomnia and so on (Mbizvo et al., 2014). Recently, LEV-induced cADRs is gradually attracting attention. It was estimated that the overall incidence of LEV-induced rashes in children and adults is about 0.6% (Arif et al., 2007). However, Wang et al. demonstrated a much higher incidence of LEV-induced skin rashes of approximately 1.65% in a group of 3793Chinese epilepsy patients (Wang et al., 2012), indicating that LEV-induced cADRs