

Spectrum of Cutaneous Adverse Reactions to Levetiracetam and Human Leukocyte Antigen Typing in North-Indian Patients

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Background and Purpose: Aromatic antiepileptic drugs are frequently implicated for cutaneous adverse drug reactions (cADRs); there are case-reports of even severe reactions like drug reaction eosinophilia and systemic symptoms (DRESS) and Stevens Johnson syndrome (SJS)-toxic epidermal necrolysis with Levetiracetam (LEV). Certain human leukocyte antigen (HLA)-alleles have strong association with cADRs due to specific drugs - HLA-B*15:02 and HLA-A*31:01 in Carbamazepine (CBZ)-related SJS in Han-Chinese and European populations, respectively. Here, the spectrum of cADRs to LEV was studied, and HLA-typing in patients with cADRs due to LEV and some who were LEV-tolerant was performed, in an attempt to find an association between HLA and such reactions.

Methods: 589 patients taking LEV were screened for skin reactions, and eight patients with LEV-related cADRs and 25 LEV-tolerant controls were recruited - all 33 of North Indian ethnicity, their HLA-A, B, DRB1 genotyping done. Statistical analysis was done to compare carrier-rates and allele-frequencies of HLA-alleles between cases and controls (and healthy population, where necessary) for alleles occurring more than two times in either group.

Results: Out of 589 patients on LEV screened, there were 8 cases of cADR: 5 with maculopapular exanthema (MPE), 2 of SJS, and 1 with DRESS. Although HLA-A*33:01 was seen to occur more in MPE cases as compared to tolerant controls, the difference was not statistically significant (odds ratio [OR] 6.00, 95% confidence interval [CI] 0.30-116.6; $p = 0.31$). HLA A*11:01 and 24:02 were found to occur more in LEV-tolerant controls than in cases (OR 0.23 [95% CI 0.02-2.36, $p = 0.33$] and 1.00 [95% CI 0.09-11.02, $p = 1.00$] respectively).

Conclusions: Cutaneous reactions to LEV are very unusual, and their association with HLA in North-Indian population was not statistically significant. (2016;6:89-94)

Key words: Levetiracetam, Maculo-papular exanthem, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Human leukocyte antigen (HLA)

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Introduction

Cutaneous adverse drug reactions (cADRs) are commonly associated with antiepileptic drugs (AEDs) particularly the aromatic Carbamazepine (CBZ), Phenytoin (PHT), Phenobarbitone (PB), and Lamotrigine (LTG). They range from minor maculopapular exanthem (MPE) to severe life-threatening reactions like Drug reaction eosinophilia and systemic symptoms (DRESS), Stevens Johnson Syndrome (SJS) and Toxic epidermal Necrolysis (TEN), and manifest within a few

hours to weeks of the AED being initiated. In a study by Sharma et al, out of 500 patients with cADRs with all drugs, anticonvulsants - PHT, CBZ and PB were implicated in 41.6% of patients with maculopapular rashes and 43.8% of life-threatening reactions - TEN and SJS.¹ Although non-aromatic AEDs like Topiramate (TPM) and LEV are thought to be safer, there are several reports of even severe cADRs like SJS, DRESS due to LEV.²⁻⁴ In 2011, the United States Food and Drug Administration (US-FDA) included serious cADRs as potential safety risk from LEV in both paediatric and adult population.⁵

Cutaneous reactions to certain drugs including anticonvulsants have shown to have strong association with specific human leukocyte antigen (HLA) alleles - HLA-B*15:02 with CBZ-related SJS/TEN in the Han-Chinese, HLA-A*31:01 in European people.^{6,7} CBZ has been also found to be the causative drug in many other populations. Therefore, it is now recommended that HLA screening for HLA-B*15:02 be done in the susceptible ethnic groups prior to initiation of the potentially offending drugs. Most of the studies with HLA typing in cADRs due to AEDs have been in CBZ-induced cases or those related to PHT or LTG, probably because of their much more frequent occurrence. In our study, we screened patients on LEV and performed HLA-typing of North Indian patients with a skin reaction to it, in an attempt to find a possible HLA-association with LEV-induced cADR in this population.

Methods

Patient enrolment

Five hundred and eighty-nine consecutive patients of epilepsy on LEV, presenting to the Neurology Outpatient Clinic or Emergency Department of the All India Institute of Medical Sciences (AIIMS) hospital between February 2013 and March 2015 were screened. All those developing skin rash, mucosal ulcers or both, within three months of initiation of LEV were recruited. These patients were all from the North Indian states of Bihar, Uttar Pradesh, Delhi, Haryana or Punjab. Dermatologist's opinion was taken to confirm the cutaneous drug reaction and to classify the same. Twenty-five patients, also from one of the above-mentioned North-Indian states, who had no skin reactions to LEV even after six months of taking the drug

were enrolled as controls. A written informed consent was taken from all subjects, and the study was approved by the Institutional Ethics Committee. History, general physical, neurological and dermatological examination findings were recorded in a proforma.

HLA genotyping

5 mL blood sample was drawn from all recruited subjects; De-oxy-ribonucleic acid (DNA) was extracted and checked for quality and quantity on 0.8% Agarose gel and spectrophotometer. HLA-A, B and DRB1 allele typing was done by Luminex based SSO technology (Lab type SSO HLA-B, A and DRB1 kits).

Statistical analysis

Two-tailed Fisher's exact test was done to determine statistical significance of the difference in carrier-rates between cases of MPE and controls for alleles occurring more than two times in either group. Also, odds ratio (OR) and allele frequency (AF) - number of times the allele is present in the sample divided by twice sample-size, expressed as a percentage - were calculated for these alleles.

If the AF was higher among tolerant controls than cases, the two-tailed Fisher's exact test was done to find statistical significance in the difference of carrier-rates and AFs in the former group and in a healthy North Indian population.

Results

Out of the 589 patients on LEV, 107 were on monotherapy and 482 on polytherapy. In all, eight patients developed cADR to LEV and were recruited as cases; of these, five were on LEV monotherapy and

Table 1. Clinical characteristics of cases with LEV-induced cADR

	Age (years)/ Gender	Diagnosis	Phenotype	Dose at which cADR occurred	Latency to cADR (days)	Concurrent Drug
Case 1	38/M	LRE-Right parietal lobe NCC	MPE	500 mg twice a day	15	Nil
Case 2	45/F	LRE-left frontal lobe NCC	MPE	1,000 mg twice a day	13	Nil
Case 3	14/F	LRE-left frontal FCD	MPE	250 mg twice a day	7	CBZ taken without cADR for 1year
Case 4	18/F	JME	SJS	250 mg twice a day	10	Nil
Case 5	24/M	JME	SJS	500 mg twice a day	7 days	Nil
Case 6	22/F	JME	DRESS	750 mg twice a day	15days	OXC, LTG
Case 7	24/F	LRE-Post stroke	MPE	500 mg twice a day	15days	Clopidogrel, Losartan.
Case 8	22/F	Idiopathic generalized epilepsy	MPE	1,000 mg twice a day	5days	Nil

LEV, levetiracetam; cADR, cutaneous adverse drug reaction; LRE, localization-related epilepsy; NCC, Neurocysticercosis; MPE, maculopapular exanthem; SJS, Stevens Johnson syndrome; FCD, focal cortical dysplasia; CBZ, Carbamazepine; JME, juvenile myoclonic epilepsy; DRESS, drug reaction eosinophilia and systemic symptoms; OXC, Oxcarbazepine; LTG, lamotrigine.

three on polytherapy. Mean age of the cases was 25.23 (range 14-45 years), there were six females and two males; their clinical features are tabulated (Table 1). Of the 25 controls, 13 were female and 12 were male; mean age was 26.68 (range 13-54 years), and twelve were on LEV alone, rest were also on other AEDs. None of the recruited subjects had a history of cADR to any drug previously.

HLA-A*11:01, 24:02, 33:01, 33:02, 68:01, 26:01, 01:01, 02:01 HLA B*7:02, 35:01, 40:01, 40:02, 40:06 15:01, 44:02 and HLA DRB1*15:01, 15:02 07:01, 13:01, 14:01, 10:01 were the alleles that occurred more than twice in the MPE cases and/or the control-groups; their AF and OR are presented in Table 2.^{8,9} When the Fisher exact test was applied to carrier rates and AFs between the groups, the differences were not statistically significant (Table 2), The AF's of HLA-A*11:01 was higher in tolerant controls (26% versus

10% in MPE cases and 12.5% in healthy population), and HLA-A*33:01 was higher among MPE cases (20% versus 2% and 0.05% in tolerant controls and healthy population respectively). HLA-DRB1*13:01, 07:01 and 15:01 were also found to be more in tolerant controls than MPE cases (OR 2.66 [95% CI 0.34-20.50, $p=0.56$]; OR 2.66 [95% CI 0.34-19.06, $p=0.36$]; OR 0.27 [95% CI 0.02-2.77 $p=0.62$]).

However, the differences in occurrence-rates of alleles between MPE cases and tolerant controls were not statistically significant. Notably, one case of SJS was positive for HLA-B*15:02 in our study, and had been on CBZ for over a year before that without any cutaneous reactions. The four digit alleles of all the 33 subjects have been tabulated (Table 3).

Table 2. Allele frequencies and odds ratios of alleles occurring more than twice in MPE cases and/or control-groups

Alleles	Allele frequency (%)		Odds ratio	95% CI	Fisher exact test- p -values Cases vs. Controls	Allele frequency in normal population (%)
	Cases	Controls				
HLA-A*11:01	10	26	0.23	0.02-2.36	0.33	12.5 [*]
HLA-A*33:01	20	2	6.00	0.30-116.6	0.31	0.50 [†]
HLA-A*33:03	20	6	1.83	0.15-22.36	0.53	8.65 [*]
HLA-A*24:01	10	6	1.83	0.15-22.36	0.53	11.1 [†]
HLA-A*24:02	10	10	1.00	0.09-11.02	1.00	19.2 [*]
HLA-A*68:01	10	6	1.83	0.15-22.36	0.53	1.92 [*]
HLA-A*26:01	10	4	2.87	0.20-39.68	0.43	1.92 [*]
HLA-A*01:01	0	6	0.58	0.02-13.05	1.00	11.5 [*]
HLA-A*02:01	0	8	0.43	0.02-9.34	1.00	5.77 [*]
HLA-B*07:02	30	10	6.00	0.78-46.14	0.10	3.84 [*]
HLA-B*15:01	0	8	0.43	0.02-9.34	1.00	1.92 [*]
HLA-B*44:02	30	10	6.00	0.78-46.14	0.10	1.92 [*]
HLA-B*35:01	10	6	1.83	0.15-22.36	0.53	7.69 [*]
HLA-B*40:01	10	6	1.83	0.15-22.36	0.53	0.96 [*]
HLA-B*40:02	0	10	0.33	0.01-7.11	0.55	1.10 [*]
HLA-B*40:06	0	4	0.85	0.03-20.45	1.00	15.4 [*]
HLA-B*50:01	0	8	0.43	0.02-9.34	1.00	1.92 [*]
HLA-DRB1*15:01	10	22	0.27	0.02-2.77	0.62	14.8 [*]
HLA-DRB1*15:02	0	6	0.58	0.02-13.05	1.00	7.4 [*]
HLA-DRB1*07:01	30	20	2.66	0.37-19.06	0.36	9.25 [*]
HLA-DRB1*13:01	20	10	2.66	0.34-20.50	0.56	1.85 [*]
HLA-DRB1*10:01	10	8	1.31	0.11-15.03	1.00	3.7 [*]
HLA-DRB1*14:01	0	4	0.85	0.03-20.45	1.00	0.92 [*]
HLA-DRB1*04:01	10	4	2.87	0.20-39.68	0.43	0.92 [*]

MPE, maculopapular exanthem; HLA, human leukocyte antigen.

[†]Ref.8; ^{*}Ref.9.

Table 3. 4-digit HLA allele of all 33 subjects

	HLA-A (Allele 1)	HLA-A (Allele 2)	HLA-B (Allele 1)	HLA-B (Allele 2)	HLA-DRB1 (Allele 1)	HLA-DRB1 (Allele 2)
Case 1	33:01	68:01	35:03	40:01	13:01	14:04
Case 2	03:02	26:01	07:02	07:02	07:01	10:01
Case 3	24:02	33:01	07:02	44:02	13:01	15:01
Case 4	02:03	02:11	15:02	40:06	15:01	15:02
Case 5	11:01	68:01	07:02	15:01	15:01	15:01
Case 6	11:01	68:01	13:16	52:01	04:01	14:01
Case 7	11:01	24:01	44:02	44:02	07:01	07:01
Case 8	32:01	33:03	18:01	35:01	04:01	11:01
Ctrl 1	01:01	24:01	35:01	52:01	12:02	15:02
Ctrl 2	11:01	11:01	35:03	44:02	13:15	14:19
Ctrl 3	02:11	11:01	40:02	41:01	11:01	14:01
Ctrl 4	02:05	11:01	07:02	44:02	15:01	15:02
Ctrl 5	26:01	31:01	44:02	51:01	15:01	15:01
Ctrl 6	02:01	33:01	13:01	15:01	04:06	13:01
Ctrl 7	11:01	24:02	18:01	52:01	15:01	15:01
Ctrl 8	11:01	11:01	15:01	40:02	04:08	07:08
Ctrl 9	11:01	24:02	15:01	40:06	10:01	12:01
Ctrl 10	24:02	24:07	15:02	40:06	15:01	15:02
Ctrl 11	32:01	33:03	07:02	40:02	13:01	15:01
Ctrl 12	11:01	24:02	15:01	40:02	10:01	12:01
Ctrl 13	11:01	68:01	07:02	40:02	04:01	07:01
Ctrl 14	24:02	26:01	07:02	44:02	07:01	15:01
Ctrl 15	03:01	03:01	50:01	57:01	03:01	07:01
Ctrl 16	02:01	11:01	13:01	50:01	10:01	13:01
Ctrl 17	24:01	68:01	07:02	50:01	07:01	07:01
Ctrl 18	03:01	24:01	35:01	40:01	07:01	11:01
Ctrl 19	03:01	33:03	35:01	44:02	04:01	07:01
Ctrl 20	30:01	68:01	51:01	53:01	13:01	14:01
Ctrl 21	01:01	02:01	37:01	53:01	10:01	13:01
Ctrl 22	01:01	24:06	52:01	57:01	03:01	07:01
Ctrl 23	11:01	33:03	40:01	52:01	14:07	15:01
Ctrl 24	02:01	03:01	40:01	52:01	07:01	15:01
Ctrl 25	01:02	11:01	50:01	57:01	03:01	15:01

HLA, human leukocyte antigen.

Table 4. Case series and reports of cutaneous adverse effects related to LEV

Serial number	Case detail	Type of cADR	Reference number
1	Neonate with perinatal asphyxia, pneumothorax	Erythematous rash and anaphylactic reaction	10
2	33 year old lady with drug-refractory epilepsy	Angioedema	11
3	55 year old man with intracranial haemorrhage	DRESS	12
4	2 cases of 20 and 29 year old women with epilepsy	TEN	4
5	2.25 year old female after surgery for congenital heart disease and SJS cardiorespiratory arrest		2
6	18 year old man	DRESS	3
7	64 year old man with basal ganglia mass	Morbilloform rash	13
8	5 Cases	Hair loss	14
9	2 cases with epilepsy- 19 year old woman, 29 year old man	MPE, Morbilliform rash	15

LEV, levetiracetam; cADR, cutaneous adverse drug reaction; SJS, Stevens Johnson syndrome; DRESS, drug reaction eosinophilia and systemic symptoms; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthem.

Discussion

Cutaneous drug reactions due to LEV are rare, and only case reports and small series are published (Table 4).^{2-4,10-15} In a systematic review of ten randomised controlled trials by Mbizvo et al, adverse effect profile of LEV in patients of drug-resistant epilepsy was studied, and rash due to LEV was reported in only two studies. It was noted that only symptoms affecting more than 5 or 10% of participants of the groups were published in these ten trials.¹⁶ In the study by Cheung et al, out of 55 patients of cADR due to various AEDs identified over 16.5 years, there was only one patient with rashes due to LEV, though one of the reasons maybe that being a newly introduced AED it may not have been prescribed much in the initial few years.¹⁷ Out of 589 patients screened in our study over two years, there were only eight cases of cADRs - this explains the small sample-size of cases. Two of the patients with skin reactions had SJS - though severe cutaneous drug reactions like SJS/TEN and DRESS are much less common than MPE. Both our SJS patients were on LEV monotherapy at onset of the symptoms therefore likelihood of the reaction being LEV-induced is high; most case-reports of these life-threatening cADRs with LEV are of patients on other drugs also, including AEDs.

Association of HLA alleles has been studied mainly in aromatic AEDs, as they are the cause of most cADRs, in particular CBZ, and certain HLA alleles predispose patients of some ethnicities to specific cADRs due to AEDs. In the European and the Chinese populations, presence of the allele HLA-A*31:01 appears to predispose to CBZ-induced DRESS, as found in an international study and meta-analysis.¹⁸ HLA B*15:02 is associated with SJS and TEN due to CBZ intake in Han Chinese population, but not with MPE.⁶ Evidence from another meta-analysis of nine case-control studies by Li X et al shows significant association between HLA-A*15:02 and PHT and LTG-induced SJS/TEN.¹⁹ A pilot-study showed that the same allele may be associated with OXC-induced mild cutaneous reactions.²⁰ It was shown in a prospective study of 252 patients, 5 developed cADRs to OXC. Out of these 5 patients, 1 was positive for HLA-B*15:02.²¹ In our study we have noted seen that HLA-A*33:01, though not statistically significant, is present in cases of MPE compared to controls (OR = 6). The p -values were not significant (0.31), when differences in AF or carrier rates were considered for calculation, and the confidence intervals may have been wide, due to the small sample size of cases.

Studies have shown HLA-B*15:02 to be associated with SJS in Indians as well. Mehta et al found 6 out of 8 CBZ-induced SJS patients from the western state of Gujarat HLA B*15:02 positive, but

none among 10 healthy controls. Other studies were on North and South Indian origin patients in which also a significant association was found between the presence of this allele and SJS due to CBZ.^{22,23} However, one of our SJS patients was positive for HLA-B*15:02. Interestingly, she had been on CBZ for over a year without any skin or mucosal reactions, and recovered as soon as her LEV was stopped. Since she had tested positive for this allele, she was shifted to Valproate from CBZ. None of the MPE cases came out to be positive for 15:02. The fact that India has a racially diverse population may be an explanation. Also there are probably other factors, like interaction of the HLA molecule with specific T-cell receptors also contributing to a cADR. HLA-A*31:01 was shown to be linked to all types of cutaneous reactions (MPE, DRESS and SJS) in the European population in a genome-wide association based study and Hu et al had four OXC-induced MPE cases positive for HLA-B*15:02 out of nine, significant when compared with population controls.^{7,20} A significant association of HLA-A*24:02 with LTG induced MPE was found in study of 21 Korean patients.²⁴

Possible protective effects of the presence of HLA-B*40:01 and HLA-B*58:01 have also been demonstrated on the basis of significantly higher rates of occurrence among AED-tolerant controls.¹⁷ We found HLA-A*11:01 positivity in 11 out of the 25 LEV-tolerant controls as against 3 out of eight cases, the AF being 26% and 10% respectively; the AF among healthy controls from the same North Indian states was 12.5%, which may suggest that the presence of this allele may be protective, though not statistically significant.⁸ A limitation of our study is that we did not simultaneously recruit healthy population controls. However, we have quoted published AF values from the same population for the alleles found in our cases and controls (Table 2). These studies, by Rajalingam et al and Rani et al had HLA-typing of 52 and 90 healthy North-Indian subjects respectively.^{8,9}

Another very recent study in the Chinese population, with nine cases of mild rashes due to LEV has also shown no significant association between HLA alleles and LEV-induced cutaneous rashes.²⁵

Cutaneous reactions to LEV, though quite unusual, have a wide spectrum of phenotypes including severe reactions like SJS/TEN and DRESS. HLA-A*33:01 was higher among MPE cases as compared to tolerant controls whereas HLA-A*11:01 was higher in tolerant controls than MPE cases, although neither association was statistically significant. We did not find any significant association between HLA alleles and LEV induced cutaneous drug rashes but a larger sample-size of cases in a multicentre study may be required in order to confirm the findings.

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Conflict of Interest

None of the authors has any conflict of interest to disclose.

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