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Association of cutaneous adverse drug reactions due to antiepileptic drugs with HLA alleles in a North Indian population

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ABSTRACT

Purpose: Aromatic antiepileptic drugs (AEDs) are frequently implicated in cutaneous adverse drug reactions (cADRs), a few of which are associated with certain human leukocyte antigen (HLA) alleles in some populations. We aimed to find HLA-associations with AED-related cADRs among North Indians.

Methods: North Indian subjects with cADR due to an AED, and those who were AED-tolerant were recruited as cases and controls, respectively. Genotyping for HLA-A, B and DRB1 were performed. Statistical analysis to compare carrier-rates and allele-frequencies between cases and controls (and healthy population, where necessary), was done for HLA-alleles occurring more than twice in either group.

Results: 120 cases {11 - Lamotrigine (LTG), 14 -Valproic acid (VPA), 8 -Levetiracetam (LEV), 35 -Carbamazepine (CBZ) and 52 - Phenytoin (PHT)}, and 250 controls were recruited. Presence of HLA-A*31:01 and HLA-B*51:01 were found to increase the risk of Maculopapular exanthema (MPE) due to CBZ and PHT (OR = 6.38; 95% CI: 1.46–27.75; OR = 4.60; 95% CI: 1.54–13.72, respectively). Among the severe cADRs, HLA-B*57:01(OR = 11.00 95% CI: 1.41–85.81) and HLA-DRB1*07:01 (OR = 7.25; 95% CI: 1.09–48.18) were noted to be significantly associated with CBZ-induced Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN); HLA-B *51:01 was associated with drug reaction eosinophilia and systemic symptoms (DRESS) caused by PHT (OR = 6.90; 95% CI: 1.38–34.29).

Conclusions: We found significant associations of some HLA alleles with specific cADRs to CBZ and PHT in North Indians, which may need to be tested before AED-initiation; only screening for HLA-B*15:02 may not help in this population.

1. Introduction

Antiepileptic drugs (AEDs), particularly aromatic ones like Carbamazepine (CBZ), Phenytoin (PHT), Phenobarbitone (PB), and Lamotrigine (LTG), are responsible for various cutaneous adverse drug reactions (cADRs). These vary from minor Maculopapular exanthema (MPE) to severe life-threatening reactions like Drug reaction eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which may develop within few hours to even several weeks after AED initiation. In a study by Sharma et al, out of 500 patients from epilepsy as well as non-epilepsy cohorts with cADRs to various drugs, the highest proportion of cases (22%) was found to have cADRs due to AEDs (CBZ, PHT and PB) [1]. AEDs also had a greater number of SJS/TEN cases than any other class of medication; this was also noted by another recent study [2]. Severe cADRs are rare [3–7], but can have mortality rates of 10 to 40% [8].

The association between cADRs and specific Human Leukocyte Antigen (HLA) alleles in certain ethnic groups is well documented. The carriage of HLA-B*15:02 increases the risk of CBZ-related SJS/TEN by 100-folds in the Han Chinese population, and HLA-A*31:01 is

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associated with CBZ-induced MPE in Europeans [9,10]. The United States Food and Drug Association (US-FDA) issued a 'warning' against the initiation of CBZ in patients of Asian origin, without HLA-typing [11].

A large proportion of people with epilepsy in India are on older AEDs (PB, Primidone, PHT, CBZ, and VPA) because of easy availability and affordability. Although there are published studies from our country, [12–14] the association of HLA with AED-related cADRs has not been looked into in a comprehensive manner till date. Therefore, we aimed to study the spectrum of cADRs due to AEDs and a possible role of HLA alleles in predisposing North Indian patients to such reactions.

2. Materials and methods

2.1. Patient enrolment

Patients who attended the Neurology and Dermatology outpatient departments of the All India Institute of Medical Sciences (AIIMS), New Delhi between February 2013 and August 2015 were screened for cADRs to AED(s). North Indian subjects (residing in the North Indian states for at least three generations) who developed a cADR confirmed to be due to an AED by the dermatologist (NK) were included in the study as cases. The cADRs were classified as MPE, SJS/TEN, fixed drug eruption (FDE) or DRESS by the standard criteria (Table 1) [[15], RegiSCAR]; both negative and positive provocation methods were used to confirm the cADR as being due to a particular AED [16,17]. Patients with cADRs to drugs other than AEDs were excluded. North Indian subjects who had no cADR even after 6 months of AED initiation were enrolled as controls. The study had the approval of our Institute's ethics committee, and a written informed consent was obtained from each subject. Demographic data, history and clinical examination details of all the cases and controls were recorded in proformas.

2.2. HLA typing

5 ml venous blood was drawn from each subject and stored in EDTA vials. QIAamp DNA mini-kits {250} were used for the isolation of Deoxyribonucleic acid (DNA). The quality and quantity of the isolated DNA were checked on 0.8% agarose gel and spectrophotometer. Intermediate and low-level typing for HLA-A, B and DRB1 alleles was done by the techniques: Polymerase Chain Reaction based Single Stranded Polymorphism (PCR-SSP) (HLA-Ready Gene A, B and DRB1; SSP based low resolution typing of HLA alleles) and PCR Sequence Specific Oligonucleotide (PCR-SSO). The latter was done on the Lab Scan 100 analyzer by the Luminex technique. Intermediate; low-level typing was done for all the alleles.The alleles with significantly higher allele frequencies (AFs) and/or number of carriers in either group were further analyzed for the four-digit allele by Next Generation Sequencing (NGS). HLA locus-specific amplification was performed using the NGSgo-AmpX reagents (GenDx-cat# 2841102 and 2841502) and Long-Range PCR reagents (QIAGEN- cat#206403). The regions that were amplified were exons 1–8 for HLA-A, exons 1–7 for HLA-B and exons 2–4 for HLA-DRB1. These amplicons were sequenced on Illumina HiSeq X to generate 2 × 150 base pair sequence-reads at 100X sequencing depth. The data was processed by FASTA-like algorithm using NGSengine Version 2.20.2.11108.

Table 1
Standard criteria and definitions of cADRs.

cADR	Assessment criteria
MPE & FDE	Based on clinical features, temporal association and provocation
SJS	Skin detachment < 10% of the body surface area, atypical target lesions and/or purpuric macules in wide dissemination.
TEN	Skin detachment > 30% of the body surface area, atypical target lesions and/or macules. Biopsy and Anti-nuclear antibody (ANA) tests were done to rule out Systemic Lupus Erythematosus (SLE). In case of strong suspicion of SLE, direct immunofluorescence (DIF) was done.
DRESS	Presence of at least 3 of the following criteria: Reaction suspected to be drug related with Acute skin rash (must for dermatological reference) Involvement of at least one internal organ Enlarged lymph nodes of at least two sites. Blood count abnormalities. Fever above 38 °C

2.3. Statistical analysis

Unpaired student *t*-test was performed to find the differences in age, gender and number of AEDs between cases and tolerant controls. For the alleles that occurred twice or more frequently in either group, differences in the carrier rates between the cases and controls was calculated by two-tailed Fisher's exact test. The odds ratio (OR) and the AFs were calculated for these alleles; AF was calculated as the number of times the allele was present divided by twice the number of subjects in the group, and was expressed as percentage. The differences in AFs between cases, tolerant controls and normal healthy North Indian population (unpublished data from our HLA-DNA lab) were calculated using the Fisher's exact test. In cases where there were multiple associations with one type of cADR due to one AED, the SHEsis software was used to determine the linkage disequilibrium (LD) between the two alleles [18].

3. Results

In all, 2146 persons on AEDs were screened and 120 consecutive subjects who fulfilled the inclusion criteria were included in this study: 40 (33.33%) patients were from the state of Uttar Pradesh, 26 (21.66%) from Delhi, 17 (14.16%) from Bihar, 14 (11.66%) from Haryana, 9 (7.50%) from Punjab, 5 (4.16%) from Rajasthan, 2 (1,66%) each from Assam, Himachal Pradesh, Uttarakhand and Madhya Pradesh, and 1 (0.83%) patient from West Bengal. Other relevant demographic data of these subjects are shown in Table 2. As expected, the maximum number of cADRs were due to aromatic AEDs (112/93.33%); the AED that was responsible for the highest number of cases was PHT (52/43.33%). We did not have any subject with cADR induced by the AEDs Topiramate, Zonisamide, Clobazam, Lacosamide, Oxcarbazepine, Pregabalin, PB, Gabapentin, or Vigabatrin. The phenotypes of the cADRs were as follows: 83(69.16%) had MPE, 17(14.16%) SJS/TEN, 15(12.50%) were diagnosed as DRESS, and 5(4.16%) were noted to have FDE.

250 AED-tolerant controls were recruited, and their demographic data is presented in Table 2. The data of 706 healthy North Indian subjects (378 M/328 F; mean age 27 years {range 4–48 years) was also used for analysis. The number of AED-tolerant controls recruited per drug was at least twice the number of cases on that drug.

The mean latency period for the onset of cADR was 12.79 days (2–60 days) {MPE 11.50(2–60); SJS/TEN 8.41 (3–18); DRESS 12.65 (3–60), FDE 18.6 (2–30)}.

Statistically significant associations of individual alleles with different types of cADRs, calculated by comparing carrier-rates in cases and controls are listed below:

3.1. MPE

HLA-A*31:01 was seen in 6 out of 27 MPE cases on CBZ as compared to 3 out of 70 controls (OR = 6.38; 95% CI: 1.46–27.75), and B*51:01 was found in 8 out of 30 cases in MPE induced by PHT as against 8 of the 100 tolerant controls (OR = 4.60; 95% CI: 1.54–13.72).

Table 2
Demographic profile cases and controls.

Drug	Cases					Tolerant controls				p-value* (age/gender/no. of AEDs)
	Number screened (mono-/poly-therapy)	Number (MPE/SJS-TEN/ DRESS/FDE)	Mean age (Years)	No. of females (%)	Mean number of AEDs	No.	Mean age	No. of females (%)	Mean number of AEDs	
LTG	221(13/ 208)	11(5/2/4/0)	23.63 (6–56)	7 (63.63)	4.54 (1–6)	25	27.56 (10–50)	13 (52)	1.84 (1–6)	0.97/0.52/0.73
LEV	589(107/482)	8(5/1/2/0)	25.23 (8–52)	6 (75)	1.50 (1–3)	25	26.68 (5–48)	13 (52)	1.62 (1–4)	0.72/0.52/0.90
VPA	608(149/459)	14(13/1/0/0)	24.07 (13–54)	5 (35.71)	1.64 (1–4)	30	25.68 (8–72)	13 (43.33)	2.00 (1–4)	0.60/0.50/0.74
CBZ	323(81/ 242)	35(27/6/2/0)	25.26 (6–70)	18 (51.42)	1.77 (1–6)	70	25.44 (6–72)	33 (47.14)	1.87 (1–4)	0.94/0.63/0.20
PHT	221(68/ 153)	52(31/7/8/5)	24.68 (6–72)	22 (42.30)	1.71 (1–6)	100	25.78 (8–69)	41 (41)	1.99 (1–6)	0.53/0.09/0.23

* Unpaired student *t*-test.

3.2. SJS-TEN

HLA-B*57:01 and HLA-DRB1*07:01 were found to be higher in CBZ-induced SJS/TEN cases. B*57:01 was seen in 2 out of 5 cases and 4 out of 70 controls, with an OR of 11.00 (95% CI: 1.41–85.81); DRB1*07:01 was found in 3 out of 5 cases as against 12 of 70 tolerant controls, with an OR of 7.25(95% CI: 1.09–48.18). The D value between these alleles was 0.988, but this value may be indicative of falsely high LD, as the r2 value was 0.376, due to the small number of cases.

3.3. DRESS

HLA-B*51:01 was detected in 3 out of 8 cases with DRESS caused by PHT but only in 8 of 100 tolerant controls, with an OR of 6.90 (95% CI: 1.38–34.29).

3.4. FDE

HLA-A*03:01 was higher in FDE cases caused by PHT with an OR of 2.23 and was seen in 2 out of 5 cases and in 13 of 100 tolerant controls. (95% CI: 0.40–12.24).

The AFs in cases and controls, of the most prominent alleles have been compared for all cADRs, in Table 3.

When the difference of occurrence of the above alleles was compared with that among healthy (North Indian) controls, HLA-A*31:01 and HLA-B*57:01were found to be significantly higher among the cases (p-values 0.0003 and 0.01, respectively); between tolerant controls and healthy North Indian population, the differences were not statistically significant.

When AFs and number of carriers of aromatic AEDs were compared to those of the other AEDs, we found that HLA-A*31:01 (p = 0.001, OR 5.94; 95% CI 2.06–17.10) and B*51:01 (p = 0.01, OR 2.82; 95% CI 1.24–6.41) were significant for MPE induced by aromatic AEDs.

HLA-B*15 was not found to be associated with any of the cADRs in our study; HLA-B*40 was found to have a negative association with PHT-induced cADRs.

4. Discussion

We found significant associations of some HLA alleles with cADRs due to CBZ and PHT in this case-control study with North Indian subjects. Prominently, HLA-A*31:01 and HLA-B*51:01 were found to increase the risk of MPE due to CBZ and PHT, respectively, by about four times. Among the severe cADRs, HLA-B*57:01 and HLA-DRB1*07:01 were noted to be significantly higher in CBZ-induced SJS/TEN, and HLA-B*51:01, in cases with DRESS caused by PHT, albeit with wide confidence intervals due to the small number of cases. HLA-B*57:01 was also reported recently in an Indian patient who developed urticaria with angioedema followed by acute generalized exanthematous pustulosis (AGEP) due to PHT and CBZ respectively [19]. However, HLA-B*57:01 and B*51:01 are not associated with CBZ or PHT-induced SJS, or MPE in European, Thai or Han Chinese populations [10,20,9,21]. In this study, we had only 2 cases of SJS/TEN that were positive for HLA-B*57:01, with a carrier rate of 20%; a bigger sample size may be required to confirm the association.

The established associations of HLA-B*15:02 and HLA-A*24:02 with various cADRs induced by aromatic AEDs were not noted in our study population. [9,22–24] This could be due to lower prevalence of HLA-B*15:02 in the Indian population (2–4%) vis a vis in the Han Chinese (8%) [25,26]. However, we did find that HLA-A*24 had a higher AF in CBZ-induced MPE compared to tolerant controls (p = 0.06). This finding is important, as screening only for and finding negative HLA-B*15:02 may not prevent many cADRs.

HLA-A*31:01 is known to increase the risk of MPE due to CBZ in the European population, as shown in the genome-wide association study by McCormack et al. [10]. Similar association in our study may be due

Table 3
AFs for all cADRs for the most prominent alleles.

Allele/Drug	Allele frequency (%)/p-value				Tolerant Controls Allele frequency (%)
	MPE	SJS/TEN	DRESS	FDE	
B*13:01/LTG	20/0.19	**50/0.03**	12.5/0.45	*	6.00
A*31:01/CBZ	**11.11/0.01**	0/1.00	0/1.00	*	2.14
B*51:01/PHT	**15/0.002**	14.28/0.13	**25/0.007**	20/0.07	4.00
DRB1*07:01/CBZ	14.81/0.44	**40/0.01**	25/0.31	*	10.0
B*57:01/CBZ	1.85/1.00	20/0.05	0/1.00	*	2.85
A*03:01/PHT	6.66/1.00	21.42/0.08	18.75/0.11	**40/0.005**	7.00
DRB1*14:01/PHT	**3.57/0.03**	21.42/0.21	18.75/0.40	0/0.60	11

*None of the cases had FDE.

to European admixture with the ancient Indian races [27]. Not only is this allele associated with CBZ-related MPE in the Han Chinese, Japanese, Koreans, and a mixed study population in Canada [28–31] but also with other types of cADRs like SJS/TEN and hypersensitivity syndrome (DRESS) [27,32]. A systematic review of all types of CBZ-induced cutaneous reactions and presence of HLA-A*31:01 reported a pooled OR of 9.45 (95% CI: 6.41–13.93; P < 0.00001) [33]; we also got similar results when we compared our CBZ cases and controls (p = 0.01). The Canadian Pharmacogenomics Network for Drug Safety recommends testing for HLA-A*31:01 prior to starting CBZ in patients of all ethnicities. Carriage of HLA-B*51:01 was reported to predispose to PB and PHT-related TEN in one study [34], but HLA-DRB1*14 has never been reported as being protective against PHT-induced MPE. HLA-DRB*14:01 and B*40 were found, in our results, to be higher among epilepsy controls as compared to PHT-induced MPE cases and all cADR-types taken as a group, respectively; the association was significant in the former, and close to significant in the latter allele. These alleles may have a protective effect against PHT-induced cADRs in our population; Cheung et al also found significantly higher rates of occurrence of B*40:01 among AED-tolerant controls in the Han Chinese. [35]

As expected, PHT and CBZ were the two most common AEDs associated with cADRs among our cases, with 52 and 35 cases respectively. We had 8 cases of cADRs to LEV, though no HLA allele was found significantly associated with the reactions; no other newer AED was observed to cause cADRs in our study population.

Despite the relatively low rates of cADRs due to the newer AEDs, physicians start most patients on the older AEDs, because of not only affordability but also availability issues (newer ones may not be freely available in the interiors) in our country. Hence, there is a need to have recommendations for other HLA alleles (not just HLA-B*15:02) to be tested prior to initiating certain AEDs that have high-risk particularly for the severe cADRs, a large number of which may be avoided if testing for the most important alleles becomes easily accessible and less expensive.

5. Conclusion

We found several alleles to be significantly higher in either cases or controls in North Indians that have not been reported before (except HLA-A*31:01) like HLA-A*51:01 (PHT-MPE/DRESS), DRB1*07:01 (CBZ-SJS/TEN) and HLA-B*13:01 (LTG-SJS/TEN). Therefore, screening only for HLA-B*15:02 before AED-initiation may not help in our population.

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Disclosure

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

Conflict of interest

The authors declare that there are no conflicts of interest.

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