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*HLA-A*24:02/B*51:01* haplotype and lamotrigine-induced cutaneous adverse drug reactions in Koreans

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Antiepileptic drugs (AEDs) have been known to induce cutaneous adverse drug reaction (cADR), ranging from a mild maculopapular eruption (MPE) to potentially life-threatening cADRs such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Despite studies examining mechanisms associated with human leukocyte antigen (HLA), the association between lamotrigine (LTG)-induced cADR and HLA alleles still has room to investigate. We investigated *HLA-A, -B,* and *-C* alleles in LTG-induced cADR. The medical records of four patients with LTG-induced cADR were retrospectively reviewed. All patients were treated with LTG for epilepsy. All recovered from cADR after stopping LTG treatment and receiving intensive care. HLA-A, -B, and -C genotyping was performed in all four patients using a PCR-sequence-based typing (SBT) method. Two patients had SJS, and the other two had MPE due to LTG. The range of latency to cADR after the initial LTG dose was 19–42 days. Two patients experienced cross-reactivity with other aromatic or new AEDs. Expression of the *HLA-A*24:02/B*51:01* haplotype was detected in three (75%) patients with LTG-induced cADR. The other patient carried homozygous *HLA-B*58:01* alleles. The results suggest that Korean individuals with the *HLA-A*24:02/B*51:01* haplotype may be susceptible to LTG-induced cADR. Further investigations are necessary to confirm these findings.

Introduction

Lamotrigine (LTG) is a popularly used antiepileptic drug (AED), but the use of LTG is limited because of cutaneous adverse drug reaction (cADR), although LTG commonly replaces other AEDs in clinical practice.[1] A number of studies have associated human leukocyte antigen (HLA) genotypes with an increased risk of cADR. A strong association between *HLA-B*15:02* and carbamazepine (CBZ)-induced severe cADR, Stevens–Johnson syndrome, or toxic epidermal necrolysis (SJS/TEN) has been identified in Han Chinese,[2] Thai,[3] Malay,[4] and Indian populations.[5] However, studies in Caucasian[6] and Japanese[7] populations did not show the same genetic expression, but showed an association with the *HLA-A*31:01* allele instead. In Koreans, *HLA-B*15:11* and *HLA-A*31:01* were reported as genetic factors for CBZ-induced severe cutaneous adverse reactions (SCARs) including SJS.[8] The results suggest that the genetic factors in AED-induced cADRs would exhibit ethnic specificity due to the HLA allele frequencies in different populations.

Due to the high cross-reactivity among aromatic AEDs such as phenytoin (PHT), CBZ, phenobarbital (PB), and LTG,[1] there have been a number of studies to identify risk HLA alleles for other aromatic AEDs based on the CBZ-induced cADR genetic biomarkers, *HLA-B*1502* and *HLA-A*3101*. However, no association was found between LTG-induced cADR and the two HLA alleles in Koreans.[9,10] The possible association of LTG-induced maculopapular eruption (MPE) and HLA alleles compared to LTG-tolerant patients were investigated in a Chinese population.[11] Two increased alleles, *HLA-A*30:01* and *HLA-B*13:02*, and a decreased allele, *HLA-A*33:03*, were observed in LTG-induced MPE patients as potential biomarkers in this

study. Recently, a study has shown an association between the *HLA-A*24:02/C*01:02* haplotype and LTG-induced MPE, but not in SCAR patients, in a Korean population.[10] Park at al. reported that *HLA-B*4403* was associated with lamotrigine-induced SJS/TEN in Koreans.[12] Two previous studies investigated 21 MPE and 7 SJS/TEN patients, respectively. Therefore, the role of HLA alleles in LTG-induced cADR needs further investigation in the Korean population.

In this study, we investigated the association of HLA-A, -B, and -C alleles in four patients with LTG-induced cADR in Korea.

Methods

Patients

We retrospectively reviewed the medical records of four patients who had LTG-induced cADR from 2010 to 2012 in Inje University Busan Paik Hospital, Busan, Korea. All patients were diagnosed with cADR by dermatology specialists. The causative drug was identified based on patient history. All of the patients took LTG for epilepsy. LTG-induced cADR was defined according to the following criteria: 1) occurrence within 12 weeks after first exposure to one of the implicated drugs; 2) manifestations of a cutaneous nature with a spotty, morbilliform, or maculopapular appearance; 3) exclusion of all other etiologies causing the cutaneous manifestations; and 4) amelioration of all cutaneous manifestations concurrent with withdrawal of the implicated drug. Our study was conducted with the approval of the Institutional Review Board of our hospital, and written informed consent was obtained from all patients.

HLA genotyping

Peripheral blood was collected from all four patients, and genomic DNA was extracted from peripheral blood mononuclear cells using a QIAamp Blood Mini Kit (QIAGEN, Hilden, Germany). We determined the HLA-A, -B, and -C genotypes using the PCR-SBT method (SBT Engine software version 2.20, GenDx, Utrecht, the Netherlands).

Results

All patients were of Korean ethnicity, and their age range was 26–69 years. Two patients were diagnosed with SJS, and the other two with MPE. The latency to skin rash after first exposure to LTG was 19 to 42 days, and the latency after maximum dose was 1–35 days. Two patients with MPE experienced cross-reactivity, one with phenytoin (PHT) and topiramate (TPM) (this patient had also experienced MPE due to LTG 7 years earlier), and another with CBZ about 20 days earlier (Table 1). The CBZ-induced MPE improved after stopping CBZ. None of the four patients carried the *HLA-B*15:02* allele. The three cases with cADRs (75%) were positive for *HLA-A*24:02* and *HLA-B*51:01*. Two patients, one with SJS and the other with MPE, also had *HLA-A*31:01*. Another SJS case showed a *HLA-A*24:02* homozygous genotype. Clinical characteristics and HLA class I (A, B, and C) genotypes of the four patients are presented in Tables 1–3. The patient with previous CBZ-induced cADR was positive not for *HLA-A*31:01* but for *HLA-B*58:01* as a homozygous genotype. Interestingly, this patient also carried homozygous genotypes in HLA-A *(*33:03)* and C *(*03:02)*. The two SJS patients had *HLA-A*24:02/B*51:01/C*14:02*. All patients discontinued LTG, which caused skin rash, and switched to other AEDs such as valproate (VPA), phenobarbital (PB), or levitriacetam (LEV). All recovered from the cADR after stopping LTG treatment and receiving intensive care.

Discussion

AED-induced cADR ranges from mild MPE to SCAR such as drug reaction with eosinophilia and systemic symptoms (DRESS), SJS, and TEN.[13] Particularly aromatic AEDs (PHT, PB, and CBZ) are known to be most frequently involved in cADR.[1,14] Cross-reactivity among aromatic AEDs (PHT, CBZ, oxcarbazepine, PB, primidone, zonisamide, and LTG) is high (40–80%), which may be explained by the "hapten hypothesis" or "pharmacological interaction theory."[1,15] The LTG-induced cADR incidence rate was reported to be about 10%, with most showing mild rashes and 0.1–1% with severe rashes requiring hospitalization.[10] The mechanism of cADR

Table 1. Clinical characteristics of the patients, including previous history of AED-induced MPE

ID	Sex	Age	Comorbidity	Previous AED-induced MPE			
				Drug	Dose (mg/day)	Latency (days)	Time[a]
1	M	58	Ischemic stroke	PHT	400	2	7 yrs
				LTG	50	18	7 yrs
				TPM	100	36	7 yrs
2	F	26	None	CBZ	200	4	20 days
3	M	69	Rheumatic mitral valve disease	None			
4	F	39	None	None			

AED: antiepileptic drug, MPE: maculopapular eruption, PHT: phenytoin, LTG: lamotrigine, TPM: topiramate, CBZ: carbamazepine. [a]Time period between previous AED-induced MPE and current LTG-induced cADR.

Table 2. Clinical characteristics of patients with LTG-induced cADRs

ID	Phenotype	Dose (mg/day)		Latency to cADR[a] (days)		Current drugs
		Initial	Maximum	Initial	Maximum	
1	MPE	25	25	35	35	VPA, PB
2	MPE	50	100	19	5	LEV
3	SJS	100	150	42	14	LEV, TPM
4	SJS	25	100	30	1	LEV

LTG: lamotrigine, cADR: cutaneous adverse drug reaction, MPE: maculopapular eruption, SJS: Stevens-Johnson syndrome, VPA: valproate, PB: phenobarbital, LEV: levitriacetam, TPM: topiramate. [a]Latency to cADR after initial and maximum dose.

Table 3. HLA-A, -B, and -C genotypes of the patients

ID	HLA-A*	HLA-B*	HLA-C*
1	*24:02/31:01*	*51:01/55:04*	*03:03/03:04*
2	*33:03/33:03*	*58:01/58:01*	*03:03/03:04*
3	*24:02/31:01*	*48:01/51:01*	*08:03/14:02*
4	*24:02/24:02*	*48:01/51:01*	*07:02/14:02*

is unclear, but it has been thought to be immune-mediated hypersensitivity, especially in SCAR. Thus, there have been many studies regarding associations between HLA alleles and specific drug-related cADRs.[1] In this study, we performed HLA-A, -B, and -C genotyping in four patients with LTG-induced cADR, two with SJS and two with MPE, to identify whether there was an association between HLA alleles and the LTG-induced cADRs. The results suggest that Korean individuals with the *HLA-A*24:02/B*51:01* haplotype may be susceptible to LTG-induced cADR; this haplotype was present in three of the four LTG-induced cADR patients (75%).

*HLA-B*51:01* is a known positive marker for Behcet's disease (BD),[16] but none of the three patients with this allele was diagnosed with BD. BD is a chronic relapsing multisystem vasculitis involving oral, genital, ocular, and skin lesions.[17] The etiology of the disease is unknown, but it involves both innate and adaptive immune reactions.[16] The disease susceptibility gene involving the immune system may be affected in LTG-induced cADR. The two SJS patients had *HLA-B*51:01* with *HLA-C*14:02*, which may be due to linkage disequilibrium (LD). A nonsignificant effect of *HLA-C*14* in BD patients has been described, which may be due to a possibly significant LD between *HLA-B*51* and *C*14*.[16] *HLA-A*24:02* and *B*51:01* frequencies in the Korean population are 21.65% and 8.35%, respectively.[18] The *HLA-B*51:01* allele frequency in patients with CBZ-induced severe cADR was relatively lower than that in the general population in a Japanese study.[7] The *HLA-A*24:02/B*59:01/C*01:02* haplotype was a high-risk genotype for LTG-induced severe cADR cases in the Japanese study. A protective effect of aromatic AED cross-reactivity from *HLA-A*24:02* was reported in a small Chinese study[19], but not in a Norwegian study, which showed an association with LTG-induced rash.[20] A Korean study identified three risk factor alleles, *HLA-A*24:02, C*01:02*, and *C*07:02*, and two protective alleles, *HLA-A*33:03* and *C*07:01*, for LTG-induced MPE.[10] Our patients had *A*24:02* and *C*07:02* but not *C*01:02* as risk factors, and had *A*33:03* among protective factors.

In our study, one patient with MPE from CBZ and LTG has a *HLA*33:03* homozygous genotype (ID 2 in Tables 1–3), which was reported to have a protective effect against LTG-induced MPE in both Korean and Chinese populations.[10,11] The patient did not have *HLA-B*15:02, B*15:11, B*31:01*, and *A*24:02*, but she had *HLA-B*58:01* as a homozygote; this allele was reported to be weakly associated with LTG-induced cADR in a population of European origin.[21] The patient had both risk and protective genes, but MPE occurred with the two drugs without masking, which may be due to a stronger effect of the risk gene than of the protective one, or to the effect of an unknown gene and/or non-genetic factors. The other three patients, two with SJS and one with MPE, had *HLA-A*24:02/B*51:01* alleles. In the HLA-A genotype, two among them have *HLA-A*24:02/31:01*, and one has *HLA-A*24:02/24:02*. Thus, all three patients had a known HLA-A allele pair in AED-induced cADR. The two SJS patients did not carry *HLA-B*44:03*, which was reported as a genetic risk factor for LTG-induced SJS/TEN in Koreans.[12] The MPE patient among these three showed cross-reactivity among aromatic and new AEDs, namely PHT and TPM, as well as LTG. He experienced MPE again when rechallenged with LTG. In these patients, there could be additional factors or independent genetic factors that induce cADR. Some reported risk factors for LTG-induced cADR are rapid titration, concomitant use of valproic acid, prior history of anticonvulsant-associated rash, female gender, and age less than 13 years.[22] In our study, the patients also had other factors mentioned above as risk factors in addition to genetic predisposition.

The limitations of this study included a very small number of LTG-induced cADR patients, only four including two SJS and two MPE patients, and no LTG-tolerant patient data. The other limitation was that the study focused only on HLA class I genotypes and did not include class II genotypes. However, three of the four patients (75%) had the same alleles in HLA-A and -B, which will be valuable information for future investigation of the possibility of a factor predicting or affecting LTG-induced cADR, including SJS and MPE. Prevention of cADR is very important in drug therapy for patients.

In conclusion, we found that LTG-induced cADRs can occur

in *HLA-A*24:02/B*51:01* Korean patients. Further studies of LTG-induced cADRs are needed to confirm the association with the alleles.

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Conflict of interest

The authors have declared that no conflicts of interest exist regarding this study.

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