Case Report

Cutaneous Adverse Drug Reactions to Lamotrigine and Human Leukocyte Antigen Typing in North Indian Patients: A Case Series

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Abstract

Cutaneous adverse drug reaction (cADR) has limited epidemiological data in India. The older antiepileptic drugs, i.e., carbamazepine, phenytoin, valproic acid, phenobarbitone, etc., induce severe cADRs that have a strong associated with human leukocyte antigen (HLA)-related genetic risk factors. There is also evidence of association of certain HLA alleles with lamotrigine (LTG)-induced cADRs, but this has not been reported in the Indian population. Here, we report case series of three patients with LTG-induced "Stevens-Johnson syndrome (SJS)." Their HLA-B typing was also performed which showed the presence of HLA-B*15:02 in one case with SJS.

Keywords: Hypersensitivity, lamotrigine, Stevens-Johnson syndrome, toxic epidermal necrolysis

Introduction

Aromatic anticonvulsant drugs are one of the most common causes of cutaneous adverse drug reactions (cADRs) that range from mild maculopapular exanthema (MPE) to severe life-threatening toxic epidermal necrolysis (TEN) and drug hypersensitivity syndrome.[1] Lamotrigine (LTG) is an efficacious antiepileptic drug (AED) in refractory partial and generalized seizures; it also acts as an effective mood stabilizer.[2] However, cADR to LTG is infrequent; studies report the incidence rate of between 0.1% and 1% for severe and about 10% for nonsevere cADR.[3] The chances of these adverse effects are higher when LTG is combined with valproate.[4,5]

Severe cutaneous adverse reactions (SCAR) due to LTG have been shown to be associated with human leukocyte antigen (HLA) alleles in the population.[6,7] Although there are a few reported cases of LTG-induced Stevens-Johnson Syndrome (SJS) in Indian patients with epilepsy,[8,9] there is no study with HLA typing. Here, we report a series of three cases with severe cADRs to LTG along with their HLA typing.

Case Reports

Case 1

A 16-year-old female student presented with absence seizures for 2 years of age and no significant past or family history of epilepsy or allergic disorder. The computerized tomography (CT) head and magnetic resonance imaging (MRI) of the brain were found to be normal; electroencephalography (EEG) was abnormal with diffuse cerebral dysfunction. She had been treated with clobazam 10 mg/day OD, for 1.5 years, but was still experiencing seizures about one to two in a day; therefore, LTG was added, starting with 25 mg a day, with weekly escalation, up to a dose of 100 mg/day. After 2 weeks of adding LTG, she developed fever, headaches, chills, and rash all over the body; the patient presented to the dermatology outpatient department (OPD) after 1 week of onset of the symptoms.

On examination, maculopapular lesions involving the genitals associated with itching were seen, which then spread to the trunk and then extremities in the next 3 days [Figure 1]. They became tender, and the erythematous, partially blanchable lesions took on a dusky hue over the trunk, upper limb, lower limb, and progressed to involve the face and lips (crusted plaques). No involvement of the oral cavity was noted nor were there any vesicular lesions. On the basis of history and clinical

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Table 1: Clinical characteristics and genotype in cases with lamotrigine-induced Stevens-Johnson syndrome

Cases	Age (years)/gender	Seizure type and duration	Phenotype	Daily dose	Four-digit allele
Case 1	Female	GTCS (1-2/day)	SJS overlap TEN	100 mg OD	HLA-B*15:01/HLA-B*52:01
Case 2	Female	Bipolar disorder	SJS	25 mg BD	HLA-B*15:02/HLA-B*44:03
Case 3	Male	JME	SJS	250 mg BD	HLA-B*13:01/HLA-B*13:01

TEN=Toxic epidermal necrolysis, SJS=Stevens-Johnson syndrome, GTCS=Generalized tonic-clonic seizures, JME=Juvenile myoclonic epilepsy

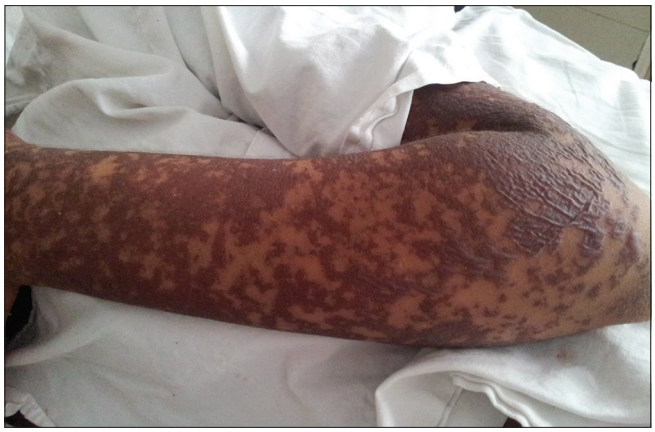

Figure 1: Large erythematous lesions on the left arm of case 1

examination, a diagnosis of TEN was made and LTG was discontinued immediately and admitted under the dermatology department. LTG was stopped, and she was started on levetiracetam 500 mg twice a day, continued on clobazam 10 mg/day, intravenous steroids, fluids, and antibiotics. With medications and supportive care, the patient improved without any further complications.

Case 2

A 54-year-old housewife, known case of bipolar disorder with anxiety, presented to the neurology OPD. She was on valproate, fluoxetine, and olanzapine but for the past 3–4 months had worsened despite being on these three medications. Mirtazapine and LTG drugs were added by the psychiatrist, 15 days after which she complained of fever, pain in both ears, and presented to the dermatology OPD with rashes. On examination multiple discrete papules which were erythematous to hyper pigmented were seen all over the body;also seen were mucosal congestion and conjunctival involvement (matted eye lashes with crusting). There was also necrosis in nasal, oral (hemorrhagic crusting on lips), and genital (moist gray-white slough on the vaginal mucosa) areas [Figure 2]. There was no past or family history of any allergies. On the basis of clinical evaluation, the patient was diagnosed with SJS. LTG was stopped immediately and appropriate treatment was initiated. Patient's general condition improved, and on discharge, she was given antibiotic, steroid, and antihistaminic medications.

Case 3

A 16-year-old boy, known case of juvenile myoclonic epilepsy, presented to the neurology OPD with generalized maculopapular rash [Figure 3], fever, and facial puffiness. He

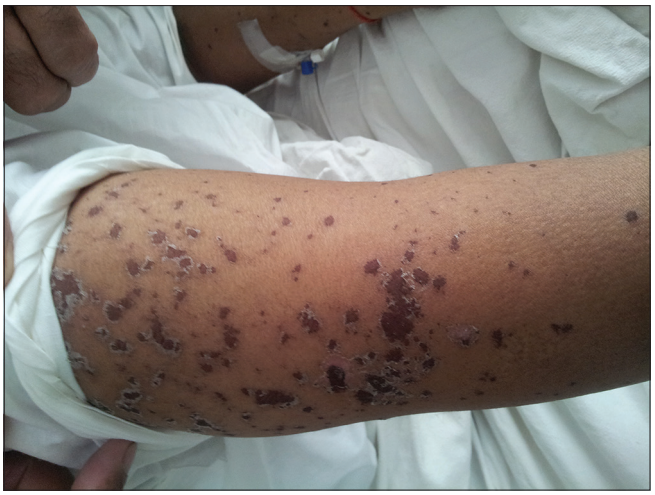

Figure 2: Multiple discrete erythematous, red macules on the limb of case 2

was on LTG 250 mg TDS, clobazam 10 mg OD, and valproate 200 mg (morning) 400 mg (evening) for 1 year. Subsequently, he developed erythematous rashes over the face, neck, trunk, arms, and legs followed by painful ulcers in the oral cavity and encrustations on the lips. History revealed that no such lesions occurred earlier. His neurological examinations, CT head and MRI, were found to be within normal limits. EEG was abnormal and suggestive of generalized epilepsy. Physical examination showed multiple round erythematous plaques on the face, neck, trunk, and extremities, some of which were tender. On oral examination, there was limited mouth opening and erythematous crusted areas on both the lips due to inflammation and ulceration. Based on the history and clinical presentation, a diagnosis of SJS was made. As the Pre-assumption was LTG, the drug was withdrawn immediately and the dose of clobazam was increased. The patient was admitted to dermatology ward and treated with cyclosporine and methylprednisolone and intravenous fluids. His condition improved during the next 2 weeks; he eventually recovered and continued follow-up on an outpatient basis.

Human leukocyte antigen genotyping

Five ml of blood sample was drawn from the patients; Deoxyribonucleic acid (DNA) was extracted and checked for quality and quantity on 0.8% agarose gel and spectrophotometer. Genotyping was done by Luminex technology by polymerase chain reaction (PCR) with sequence-specific primers (LabType SSO HLA-B kits; One Lambda, United States). High-resolution typing was done by One Lambda PCR kit by the standard protocol of the

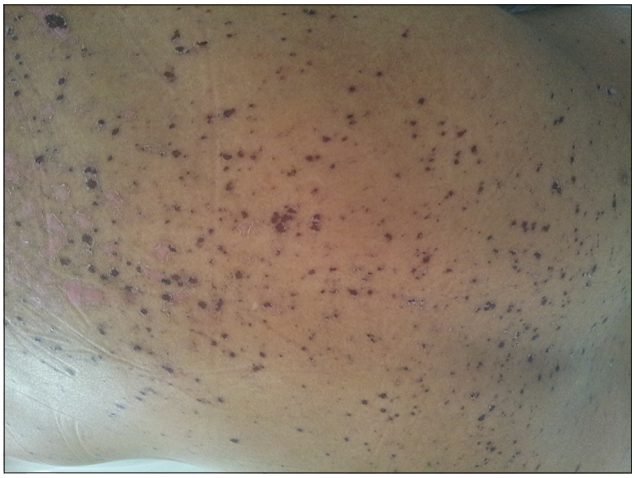

Figure 3: Macular crusting over the trunk of case 3

manufacturer. The PCR products were run on LabScan 100 analyzer for the detection of four-digit HLA alleles.

Discussion

Associations between the HLA-A*30:01 and B*13:02 alleles and LTG-induced MPE have been reported in Han Chinese.[10] Among other population groups, the HLA-B*58:01, A*68:01, Cw*07:18, DQB1*06:09 and DRB1*13:01 alleles were reported to be weakly associated with LTG-induced cADR in patients of European origin,[11] and the HLA A*02:01:01/B*35:01:01/C *04:01:01 haplotype has been suggested as a biomarker for LTG-induced MPE in Mexican mestizo patients.[12] Here, we report a series of three North Indian patients who had severe cADRs (SJS and TEN) to LTG. The alleles associated were HLA-B*15:02/52:01, HLA-B*15:02/ 44:03 and HLA-B*13:01/13:01 homologous [Table 1].

In the study done by Cheung *et al*. on 55 patients of cADRs due to various AEDs over 16.5 years, different HLA-B alleles were detected, and among all cases, HLA-B*1502, HLA-B*13:01, HLA-B*38:02, and HLA-B*46:01 were found to be the most common alleles found in Han Chinese patients.[6] Park *et al*., In a study of 5802 Korean patients, found 26 types of HLA-B alleles, the most common alleles being HLA-B*15 and HLA-B*44. After high-resolution HLA typing done in some cases, the alleles which were found to be associated with SCAR were HLA-B*44:03, HLA-B*51:01, and HLA-B*15:01.[7] Another study by Kim *et al*. on 18 patients with LTG-induced SCAR, HLA-A*31:01 was significantly higher among SCAR patients compared with the LTG-tolerant group and general Korean population.

HLA-B*15:02 Allele was found in one of our patients; the association of this allele has been reported in several studies associated with LTG-induced cADRs.[6,13] According to a meta-analysis done by Zeng *et al*., there are only six studies that have looked into the association of HLA gene with LTG -induced SJS/TEN, of which four found an association with HLA-B*15:02 in Han Chinese cases While the other two (in the European population) did not.[14] Furthermore, positive association was found between HLA B*1502 and LTG-SJS/TEN in the Han Chinese Population of in Hong Kong, Taiwan, and Mainland China in another meta-analysis.[15] Although we also found HLA-B*15:02 in one of our LTG-induced SJS/TEN patients, a case–control study must be done in the Indian population to look for the association of specific HLA alleles in LTG-induced cADRs.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ruble R, Matsau F. Anticonvulsant-induced cutaneous reactions incidence, mechanisms and management. CNS Drugs 1999;12:215-36.
2. An DM, Wu XT, Hu FY, Yan B, Stefan H, Zhou D, *et al.* Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population. Epilepsy Res 2010;92:226-30.
3. Söğüt A, Yilmaz A, Kilinç M, Söğüt AG, Demiralay E, Uzar H, *et al.* Suspected lamotrigine-induced toxic epidermal necrolysis. Acta Neurol Belg 2003;103:95-8.
4. Kocak S, Girisgin SA, Gul M, Cander B, Kaya H, Kaya E, *et al.* Stevens-Johnson syndrome due to concomitant use of lamotrigine and valproic acid. Am J Clin Dermatol 2007;8:107-11.
5. Yalçin B, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. J Am Acad Dermatol 2000;43:898-9.
6. Cheung YK, Cheng SH, Chan EJ, Lo SV, Ng MH, Kwan P, *et al.* HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. Epilepsia 2013;54:1307-14.
7. Park HJ, Kim YJ, Kim DH, Kim J, Park KH, Park JW, *et al.* HLA Allele Frequencies in 5802 Koreans: Varied allele types associated with SJS/TEN according to culprit drugs. Yonsei Med J 2016;57:118-26.
8. Naveen KN, Ravindra MS, Pai VV, Rai V, Athanikar SB, Girish M. Lamotrigine induced DRESS syndrome. Indian J Pharmacol 2012;44:798-800.
9. Kashyapa H, Verma L, Jadhav RB. Lamotrigine-induced Stevens-Johnson syndrome in a 25 year old lady. Int J Basic Clin Pharmacol 2016;5:2694-6.
10. Li LJ, Hu FY, Wu XT, An DM, Yan B, Zhou D, *et al.* Predictive markers for carbamazepine and lamotrigine-induced maculopapular exanthema in Han Chinese. Epilepsy Res 2013;106:296-300.
11. Kazeem GR, Cox C, Aponte J, Messenheimer J, Brazell C, Nelsen AC, *et al.* High-resolution HLA genotyping and severe cutaneous adverse reactions in lamotrigine-treated patients. Pharmacogenet Genomics 2009;19:661-5.
12. Fricke-Gallindo, Martinez-juarez IE, Monroy-Jaramillo N, Jung-Cook H, Falfan-Valencia R, Ortega-Vazquez A, *et al*. HLA-A*02:01:01/-B*35:01:01/-C*04:01:01 haplotype associated with lamotrigine-induced maculopapular exanthema in Mexican Mestizo patients. Pharmacogenomics.2014;15:1881-91.
13. Hassan I. HLA-B*1502 screening in carbamazepine and lamotrigine candidates of Asian background. Aust N Z J Psychiatry 2012;46:1106-7.
14. Zeng T, Long YS, Min FL, Liao WP, Shi YW. Association of HLA-B*1502 allele with lamotrigine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese subjects: A meta-analysis. Int J Dermatol 2015;54:488-93.
15. Yuying Sun and Yongzhi Xi. Association Between HLA Gene Polymorphism and Antiepileptic Drugs-Induced Cutaneous Adverse Reactions. Available at: http://www.inte chopen.com/books/hla-and-associated-important-diseases.