

Carbamazepine-Induced Stevens–Johnson Syndrome and HLA-B*1502 Screening among First-degree Relatives of Index Patients

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Abstract

Background: Carbamazepine (CBZ) is often implicated in drug-induced Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). CBZ-induced SJS/TEN is strongly associated with the HLA-B*1502 allele in Southeast Asia. **Objectives:** The objective was to determine the prevalence of HLA-B*1502 allele in patients with CBZ-induced SJS/TEN and in their first-degree relatives. **Materials and Methods:** Ten cases of CBZ-induced SJS/TEN from a single center were contacted and offered HLA-B*1502 genotyping for themselves and their first-degree relatives. Eight patients and 12 relatives consented for genotyping. **Results:** HLA-B*1502 was positive in all patients who were tested, of whom 50% of them were Malay and 50% were Chinese. The frequency of the HLA-B*1502 allele in the first-degree relatives was 58%. **Conclusion:** HLA-B*1502 is common in first-degree relatives of patients with CBZ-induced SJS/TEN.

Keywords: Carbamazepine, drug hypersensitivity, HLA-B*1502, Stevens–Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

Carbamazepine (CBZ)-induced Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is strongly associated with the HLA-B*1502 allele in Southeast Asia. This association between HLA-B*1502 and CBZ-induced SJS in Han Chinese was first reported in Taiwan in 2004.^[1]

Subsequently, this association was also reported in other Southeast Asian countries.^[2–7] The US Food and Drug Administration (FDA) has recommended HLA-B-1502 screening in patients of Asian ancestry before starting CBZ.^[8]

This study aims to investigate the prevalence of the HLA-B*1502 allele in patients with CBZ-induced SJS/TEN in Singapore and in their first-degree relatives.

MATERIALS AND METHODS

Between 2004 and 2011, there were 28 cases of SJS and TEN admitted to Changi General Hospital, Singapore, of which 10 cases were induced by CBZ. After the Institutional Review Board approval, the ten patients with CBZ-induced SJS/TEN were contacted and offered HLA-B*1502 genotyping for

themselves as well as their first-degree relatives. Five milliliters of peripheral blood was drawn from the patients into EDTA blood containers and sent to the Health Sciences Authority’s Tissue Typing Laboratory, Singapore, for HLA-B*1502 genotyping with sequence-specific primer polymerase chain reaction.

RESULTS

There were six male and four female patients [Table 1]. The mean age was 40 years, with a range of 15–73 years. There were five Malay, four Chinese, and one Filipino patient. Four patients were given CBZ for neuropathic pain, three for epilepsy, and three for mood stabilizing in schizophrenia and depression.

We were unable to contact the Filipino patient as she had gone back to the Philippines. One patient declined to participate. Of

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the eight remaining patients, HLA-B*1502 allele was present in all eight. Twenty-eight first-degree relatives were identified, of whom 12 agreed to participate. Seven of the 12 first-degree relatives (58%) had the HLA-B*1502 allele.

DISCUSSION

The HLA-B*1502 allele was present in all of the eight patients with CBZ-induced SJS/TEN in our study. This is consistent with the studies in Taiwan,^[1] Hong Kong,^[2] and Malaysia,^[6] suggesting a strong association between HLA-B*1502 and CBZ-induced SJS/TEN in Southeast Asians. In Singapore, the risk of SJS/TEN among CBZ users carrying the HLA-B*1502 allele is increased approximately 181-fold.^[9]

Of note, 50% of our study population were of Malay ethnicity. The ethnic composition of the Singapore population in 2018 was Chinese 76.1%, Malays 15.0%, Indians 7.5%, and Others 1.5%.^[10] The incidence of CBZ-induced SJS/TEN in the Malays is out of proportion to the population demographics. This finding could be due to a higher prevalence of HLA-B*1502 allele in the Malay population (14%), followed by the Chinese (11.6%) and Indians (<2%) in Singapore.^[11]

Although an association between HLA-B*1502 and CBZ-induced SJS has been reported in Indian patients, there were no Indian patients in our study. This could be explained by the smaller Indian population (7.5%) in Singapore and the low prevalence of HLA-B*1502 in the Indian population. In India, a 0–6% (average 2.5%) prevalence of HLA-B*1502 in different communities has been reported. Most of them are sub-Hindu communities, except for Parsi, in which a 0% prevalence was reported.^[4] A study which analyzed the cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore showed that providing alternative anti-epileptics to those who test positive for HLA-B*1502 is cost-effective for Singaporean Chinese and Malays but not for Singaporean Indians because of the different population allele frequencies of HLA-B*1502 among different ethnic groups.^[12]

The US FDA and similar regulatory agencies in Canada, Taiwan, and Singapore have updated the CBZ drug label to include the association observed between HLA-B*1502 allele and CBZ-induced SJS/TEN, the prevalence of this allele in various Asian populations, as well as recommendation to consider testing for the presence of HLA-B*1502 allele in patients with Asian ancestry prior to prescribing CBZ. Starting from 2013 in Singapore, genotyping for HLA-B*1502 is the standard of care prior to the initiation of CBZ therapy in new patients of Asian ancestry.^[9]

Out of our ten patients, four were prescribed CBZ for neuropathic pain, three were given CBZ as a mood stabilizer, and the remaining three were given for seizures. The indication for CBZ in seven of our patients with CBZ-induced SJS/TEN was nonurgent. It is reasonable to screen for the HLA-B*1502 allele before commencing CBZ for nonurgent medical conditions as the turnaround time for HLA-B*1502 genotyping in Singapore is between 1 and 4 working days.

In this study, first-degree relatives of index patients underwent screening for the HLA-B*1502 allele, of which the frequency was 58%. It was not determined whether they were heterozygous or homozygous for the HLA-B*1502 allele. Furthermore, there are limited data looking at the genotype–phenotype association of the HLA-B*1502 allele. From a study done in Taiwan, the gene dosage effect of the HLA-B*1502 allele was not observed, whereby homozygosity of the HLA-B*1502 allele was not associated with a greater disease severity.^[13]

CONCLUSION

In view of the high frequency of allele positivity among the first-degree relatives of patients with CBZ-induced SJS/TEN, this population should be counseled on the association of the HLA-B*1502 allele and CBZ-induced SJS/TEN and availability of genotyping. The use of CBZ should be avoided in tested people who are positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Even though SJS/TEN is rare, they are serious, potentially fatal disorders. We would like to highlight the strong association of the HLA-B*1502 allele and CBZ-induced SJS/TEN in Singapore as well as the high prevalence of the HLA-B*1502 allele in first-degree relatives of index patients. Prior to starting a patient on CBZ, it would then be helpful to inquire about a positive family history of CBZ-induced SJS/TEN.

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Conflicts of interest

There are no conflicts of interest.

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Table 1: Patient characteristics

Gender	Age	Race	Diagnosis	Indication for carbamazepine
Female	47	Chinese	TEN	Schizophrenia
Female	47	Chinese	SJS/TEN	Epilepsy
Male	73	Malay	SJS/TEN	Neuropathic pain
Male	37	Malay	SJS	Depression
Female	35	Filipino	SHS	Neuropathic pain
Male	38	Malay	SHS	Neuropathic pain
Male	15	Malay	SJS/TEN	Epilepsy
Female	25	Chinese	SJS/TEN	Epilepsy
Male	49	Malay	SJS	Neuropathic pain
Male	34	Chinese	SJS	Schizophrenia

TEN: Toxic epidermal necrolysis, SJS: Stevens–Johnson syndrome

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