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Short communication

Stratification of the risk of serious allergic cutaneous reactions with therapeutic management of trigeminal neuralgia

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Abstract

Patients with the HLA-B*1502 allele have a high risk of serious allergic cutaneous reactions from antiepileptic drugs used in the management of trigeminal neuralgia. Awareness of this uncommon but potentially fatal reaction will help to avoid the use of these drugs in patients from racial groups at high risk.

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Introduction

Trigeminal neuralgia is a severe unilateral, paroxysmal, facial pain typically described by patients as the “world’s worst pain”.¹ The onset is usually in the sixth or seventh decade of life.¹

The aim of treatment is to relieve pain. Medical management is typically with carbamazepine, and up to 70% of patients report satisfactory pain control.¹ The symptoms of the remaining 30% are usually managed with other antiepileptic drugs.¹

Serious allergic cutaneous reactions, particularly Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are among the most feared complications of antiepileptic drugs^{2–4} with the reported mortality being 30%.^{2–4}

Discussion

Chung et al. first identified an association between HLA-B*1502 and carbamazepine-induced SJS/TEN.⁵ Their later study showed a 100% association between the HLA-B*1502 allele and carbamazepine-induced SJS in Han-Chinese patients, with an extremely high odds-ratio (2504) compared with those who were carbamazepine-tolerant.⁶

This strong link suggests that the product of this gene may have a direct functional role in drug hypersensitivity. It has been proposed that the HLA-B*1502 allele codes for a molecule that is displayed on the surface of antigen-presenting cells.^{5,6} One hypothesis proposes that carbamazepine or a metabolite combined with an unknown peptide binds to a cell surface molecule, which then activates naive CD8+ T-lymphocytes, which in turn proliferate and lead to SJS/TEN.^{3,4}

HLA-B*1502 occurs with striking variability among different ethnic groups (Table 1). While only partly defined, its reported incidence includes 10–15% in Southern China, Thailand, Malaysia, Indonesia, Philippines, and Taiwan^{2,7,8}; 2–4% in the Indian subcontinent²; less than 1% in Japan and

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Table 1

The prevalence of HLA-B*1502 in major populations.^{7,8}

Continent and ethnicity	Incidence of allele (%)	No
North America:		
Asian	5	396
African	<1	251
Hispanic	0	240
European	0	287
Native American	0	235
Asia:		
Singapore	12	86
Han Chinese	10	572
Malay	8	101
Thai	6	99
India (Khandesh Pawra)	6	50
Filipino	5	94
India (North Hindi)	2	91
India (Mumbai Marathas)	1	72
Korean	<1	200

Korea^{2,7,8}; and none in white Europeans, native Americans, and Hispanics.^{7,8}

Two small studies have failed to show a correlation between HLA-B*1502 and carbamazepine-induced STS/TEN in the white population. The first showed no link between the two documented cases of STS/TEN and this allele.⁹ The second investigated 12 cases of carbamazepine-induced STS/TEN taken from the European Registry of Severe Cutaneous Reactions. Only four of the 12 French and German patients had the HLA-B*1502 allele, and interestingly all four had Asian ancestry,¹⁰ which suggests that ethnicity may have an important effect on the penetrance of this allele.¹⁰

A recent FDA alert recommends that patients with ancestry from populations with a high risk of SJS/TEN should be screened for the HLA-B*1502 allele before starting carbamazepine.² It also recommends that those with the allele should not be treated with carbamazepine unless the expected benefit clearly outweighs the risk.² Patients who have been tested and do not have the HLA-B*1502 allele have a low

risk, but SJS/TEN can still occur rarely, and all patients must be monitored closely at the start of drug treatment.

Patients with the HLA-B*1502 allele may also have a high risk of STS/TEN from other drugs used in the management of trigeminal neuralgia. Phenytoin, oxcarbazepine, topiramate, and lamotrigine have all been associated with SJS/TEN, and their use should be avoided.³ This leaves few therapeutic options and gabapentin, pregabalin, clonazepam, and baclofen are the only potentially useful medications without the associated complications¹; surgery may be the most viable option for long-term management of these patients.

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