Carbamazepine-induced Stevens-Johnson Syndrome in a Pakistani Girl with Positive HLA-A*3101 Allele

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Abstract
Carbamazepine is one of the commonest anticonvulsants that can cause cutaneous adverse drug reactions. The association of HLA-B*1502 allele with carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis has been confirmed by strong evidences. Since 2007, the Food and Drug Administration in the United States recommended genetic testing of HLA-B*1502 allele in patients with ancestry across broad areas of Asia before prescription of carbamazepine. However, HLA-B*1502 allele should not be considered as the only predication marker of Carbamazepine-induced Stevens-Johnson syndrome. Other alleles, one of them being HLA-A*3101 allele, are recently being studied on their association with drug allergic events in different populations. We report a ten-year-old Pakistani girl diagnosed to have carbamazepine-induced SJS, who had absence of HLA-B*1502 allele but presence of HLA-A*3101 allele.

Key words
Adverse drug reaction; Carbamazepine; HLA-A*3101; HLA-B*1502; Stevens-Johnson syndrome

Introduction
Carbamazepine, a commonly used anticonvulsant, can cause cutaneous adverse drug reactions ranging from mild maculopapular exanthema to life-threatening severe cutaneous reactions which includes Stevens-Johnson syndrome, toxic epidermal necrolysis and drug hypersensitivity syndrome (HSS). The incidence for isolated rash due to anticonvulsants is around 16% while that for severe cutaneous reactions is estimated to be 1.5 to 6.2 in 10,000 new users. The association between HLA-B*1502 allele and Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN) has been well established among Han-Chinese and in some Asian populations including Thais and Malaysians. With over 90% of the population being Chinese descent, proactive measures were adopted by the Hospital Authority since September 2008 requesting mandatory HLA-B*1502 gene testing prior to prescribing carbamazepine to the new patients. However, HLA-B*1502 status should not be used as the sole predication marker of carbamazepine-induced allergic reactions in all ethnics groups. We herein report a case of a Pakistani girl with carbamazepine-induced SJS who was tested negative for HLA-B*1502 allele but positive for HLA-A*3101 allele.

Case Report
Our patient, a Pakistani girl, born by normal spontaneous delivery at full term in Hong Kong, had unremarkable antenatal and postnatal history. Her sister was an epileptic since infancy. Our patient first presented at 6 months of age with recurrent episodes of generalised tonic-clonic seizures. No secondary causes could be identified. The epileptic condition was well controlled by phenobarbitone. However, the patient stopped taking medication one year afterwards and defaulted to attend further medical follow-ups.
At 10-year of age, our patient presented to us for breakthrough generalised tonic-clonic convulsions of four times over a six-week period. She also suffered from frequent short-lasting episodes "being not able to move" for around 30 times per day over the previous two years, precipitated by postural changes with consciousness maintained. Investigations including the computerised tomography of brain and the electroencephalography were both unremarkable. The diagnosis of paroxysmal kinesigenic dyskinesia was established by the neurologists. The HLA-B*1502 status was tested negative and thus carbamazepine was started for both dyskinesia and epilepsy.

One month after the commencement of carbamazepine, this Pakistani girl was admitted to our paediatric ward again for acute onset of fever, skin rash and sore throat. The child was malaise and febrile with the body temperature rose up to 39.3 degrees Celsius. Generalised, blanchable erythematous maculopapular rash was found over her face and trunk and a congested throat without tonsillar exudates or oral ulcers was also detected. Physical examination of other body parts reviewed no abnormalities. Blood tests including the complete blood count, renal function test and anti-streptolysin O titre were all normal, while liver function test showed a slightly elevated alanine transaminase 36 IU/l (<33 IU/l) as well as an elevated C-reactive protein 28.4 mg/l (<8.2 mg/l). Complements C3, C4 were normal, rheumatoid factor and anti-nuclear antibody were negative. No bacterial was grown from the blood culture and throat swab, or any virus could be isolated from the nasopharyngeal swab.

Penicillin was prescribed for a provisional diagnosis of scarlet fever. However, the girl had persistent high fever and generalised painful maculopapular skin rash spreading from trunk to limbs. Carbamazepine was discontinued for suspected drug allergy on the next day. As her HLA-B*1502 status was negative, in view of patient's ethnicity and a high suspicion of carbamazepine allergy, the HLA-A*3101 allele was tested and was confirmed positive subsequently.

Her fever and facial rash gradually subsided after discontinuation of the offending drug. Yet, over the next few days, rash over limbs increased, blisters developed over her swollen fingers and even faint dark discoloration was found over the left thumb. Painful mucosa involving eyes, oral cavity, vulval and perianal regions also evolved. Oral ulcers developed and she once complained transient microscopic haematuria with painful micturition. Although skin biopsy was not done, the diagnosis of SJS secondary to carbamazepine was ascertained clinically.

Symptomatic treatment including painkiller, eye drops for lubricating of eyes, mouth gargle were offered. All skin and mucosal lesions resolved two weeks later. Mild detachment of skin over the old blisters was found on the fingers which recovered completely with time. Sodium valproate was adopted to control both dyskinesia and seizure attacks. The patient had remained seizure-free and decreased dyskinesia episodes, without any adverse drug reactions.

**Discussion**

Anticonvulsants are one of the commonest causes of drug-related cutaneous adverse drug reactions, ranging from maculopapular exanthema to severe conditions including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug hypersensitivity syndrome. In fact, carbamazepine was reported to be the most notorious drug (25-33% of cases) associated with SJS/TEN in Asians, whereas only 5-6% of Caucasian cases are caused by it. The overall estimated risk of carbamazepine-induced serious cutaneous reaction is 1.5 to 6.2 per 10,000 new users according to the Caucasian studies, mostly occurred within the initial two months of anticonvulsant usage. However, the risk varies largely among different populations and has been reported at a much higher rate in some Asian populations.

The strong association of HLA-B*1502 allele with carbamazepine-induced SJS/TEN was initially reported among the Han Chinese patients in Taiwan and Hong Kong, which was further proclaimed by the other Asian studies including Thailand and Malaysia. In 2004, Chung et al recruited 44 Han-Chinese patients with Carbamazepine-induced SJS, 101 Carbamazepine-tolerant patients and 93 healthy controls without Carbamazepine usage in Taiwan. All 44 SJS cases carried HLA-B*1502 allele while only 3% in Carbamazepine-tolerant group. The odds ratio of carbamazepine-induced SJS versus carbamazepine-tolerant group is 2504 which is extremely high (95% CI 226-49522). In Hong Kong, a previous study has reported the association between HLA-B*1502 with SJS/TEN induced by anticonvulsants, which included carbamazepine, phenytoin and lamotrigine with odds ratio 71.9 (95%CI 3.7-1415.8). However, the Food and Drug Administration in the United States has not yet recommend a mandatory screening on the HLA-B1502 allele before starting anticonvulsants other than Carbamazepine due to limited data up-to-date.
Interestingly, the allele frequency of HLA-B*1502 was very low (0.2% compared with 8.6% in Han Chinese in Taiwan) among the Japanese and hence may explain the absence of association between the presence of this allele and carbamazepine-induced SJS/TEN. An European study by Lonjou et al found that among 12 carbamazepine-induced SJS/TEN cases (nine French and three German), only four of them had HLA-B*1502 allele among whom were of Asian origin. Thus the authors concluded that HLA-B*1502 allele should not be considered as a universal prediction marker in all ethnic groups.

In 2007, the Food and Drug Administration in the United States recommended genetic testing of HLA-B*1502 allele in patients with ancestry across broad areas of Asia before prescribing carbamazepine. In Hong Kong, the Hospital Authority started a mandatory HLA-B*1502 gene testing for new patients who required carbamazepine treatment as proactive measures to prevent severe drug reactions in 2008. Studies have been carrying on worldwide searching for other alleles that can be a potential genetic predictor for severe carbamazepine-induced cutaneous adverse reactions in other ethnic groups. In 2011, McCormack et al reported a genome-wide association study among subjects of Northern European ancestry and confirmed the association of HLA-A*3101 allele with carbamazepine-induced hypersensitivity reactions. Such reactions included the relatively mild maculopapular exanthema to more severe reactions, such as SJS, TEN, and HSS. When present, the overall risk was increased from 5.0% to 26.0% while its absence reduced the risk from 5.0% to 3.8%. This finding was echoed by a Japanese group who also found that HLA-A*3101 allele was a significant predictor for carbamazepine-induced cutaneous adverse drug reactions with 60.7% sensitivity and 87.5% specificity.

The associations between HLA-B*1502 and HLA-A*3101 with carbamazepine-induced skin reactions illustrated the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions and even liver injury.

In our case, the Pakistani girl with carbamazepine-induced SJS had absence of HLA-B*1502 allele but presence of HLA-A*3101 allele. The prevalence of this allele is 2 to 5% in Northern European populations, 2% in Han Chinese populations, and 9% in Japanese populations. To our knowledge, the prevalence of HLA-B*1502 and HLA-A*3101 in Pakistani population have not been well studied, thus further studies are deemed necessary. Additional work is also required to determine whether the effect of the HLA-A*3101 allele is specific to carbamazepine or whether it also applies to other drugs. Nevertheless, our patient did not develop any side effects related to sodium valproate.

Conclusion

HLA-B*1502 allele should not be considered as the only prediction marker for carbamazepine-induced severe cutaneous allergic reactions in all ethnic groups. With more studies confirming the association between the adverse drug reactions and the presence of HLA-A*3101 allele, a need is urged for further studies on the prevalence of these two alleles and the usefulness of using these as prediction markers among various ethnic groups. Moreover, with an advancement in HLA-genotyping and understanding on their clinical correlations, further evaluations on other alleles in Carbamazepine-induced SJS Han-Chinese patients with negative HLA-B*1502 may also be worthwhile.

Declaration of Interest

None

References