

Hypersensitivity to Antiepileptic Drugs

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KEYWORDS

- Antiepileptic drugs • Drug hypersensitivity • Pharmacogenetics
- Severe cutaneous adverse reactions

KEY POINTS

- Antiepileptic drug allergy is a rare but potentially fatal adverse reaction, associated most commonly with phenytoin, carbamazepine, and lamotrigine.
- Antiepileptic drug allergy generally occurs on first exposure to the drug, with symptoms such as skin rash, fever, and internal organ involvement that develop within several weeks of drug exposure.
- Early diagnosis is essential because primary treatment starts with cessation of the implicated drug.
- Avoidance of other aromatic anticonvulsants (eg, phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, and lamotrigine) is recommended in patients who develop allergic reactions to any one of these agents due to a high degree of cross-reactivity among them.
- Pharmacogenetic testing for HLA allele B*1502 should be considered before commencing carbamazepine in Han Chinese, South Asian, and East Indian patients.

INTRODUCTION

Adverse reactions to antiepileptic drugs (AEDs) may lead to treatment failure, morbidity, and mortality from both epilepsy and the adverse drug reaction (ADR).^{1,2} It may also impair the quality of life for epilepsy patients.¹ Most adverse reactions to AEDs are predictable, dose-dependent, and pharmacologic-associated type A ADRs, which are usually reversible after discontinuation of the offending drugs. However, type B ADRs occur unexpectedly in susceptible patients and are pathogenically unrelated to the mechanism of action of the drugs. Despite the relatively low

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incidence, drug hypersensitivity reactions (DHRs) that are type B may result in potentially fatal outcomes.³ As for antibiotics, conventional aromatic AEDs are a common cause of drug allergy (immunologic-mediated DHRs) in hospitalized and general populations.^{4,5} AED DHRs present with a variety of different clinical manifestations ranging from skin rashes and mucosal involvement to systemic involvement (fever, hepatitis, lymphadenopathy, eosinophilia, and blood dyscrasias). Cutaneous eruptions are the more common manifestation. However, severe cutaneous adverse reactions (SCARs) are not rare in AED users.² These include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DIHS), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). The pathogenesis of AED DHR has not been fully elucidated. Bioactivation, detoxification, covalent adduct formation, presentation to the immune system, and consequent formation of antibody and T-cell immune effectors have been suggested.⁶ The incidence and severity of AED DHRs may be affected by various factors that include age, gender, genetics, and the drug itself.² Identifying susceptible individuals and risk factors, as well as close clinical monitoring during the latent period are key to the prevention of AED DHR. This article summarizes the epidemiology, pathogenic mechanisms, risk factors, clinical features, and management of allergic reactions to the aromatic AEDs carbamazepine (CBZ), phenytoin (PHT), and lamotrigine (LTG).

EPIDEMIOLOGY

The prevalence of DHRs to AEDs varies according to the populations enrolled, offending drugs, and study design. Skin rash is a common adverse reaction of AEDs and is a leading cause of withdrawal from some AED trials.⁷

A retrospective chart review reported that the average rate of AED-associated rash was 2.8%, resulting in a rate of AED discontinuation of 2.1%.⁸ Most reports on ADRs to AEDs have shown higher rates of rash with CBZ (5%–17% of the patients taking CBZ), PHT (5%–7%), and LTG (5%–10%).⁸ Severe mucocutaneous reactions with internal organ involvement such as DIHS-DRESS and SJS-TEN are estimated between 1 in 1000 and 1 in 10,000 exposures.⁹ The incidence of AED DHRs in patients with head injuries increases to 1 in 100.¹⁰

SJS-TEN can lead to significant disability or mortality (ranging from 10% to 40%) despite the low incidence.¹¹ Aromatic AEDs (including CBZ, PHT, phenobarbital, and LTG) are also associated with these SCARs.⁹ In addition, aromatic AEDs are significantly associated with IgE-mediated (immediate) type I and cell-mediated (non-immediate or delayed) type IV DHRs, with a reported odds ratio of 2.15 and 6.06, respectively.¹²

Cross-sensitivity among aromatic AEDs (particularly high in female patients) is reported to be 30% to 58%.^{8,13} Among various AEDs, PHT and CBZ were reported as the two drugs with the most frequent cross-reactivity.¹³ In addition, cross-reactivity between CBZ and tricyclic antidepressant agents has also been reported based on their structural similarity with the tricyclic nucleus.¹⁴

RISK FACTORS

Genetic Factors

Genetic markers are useful to predict individuals susceptible to AED DHR (**Box 1**). HLA alleles represent a major determinant of AED DHR since 2004 when Chung and colleagues¹⁵ first reported a strong association of HLA-B*1502 in Han Chinese patients with CBZ-induced SCARs. This strong association was further confirmed by other

Box 1**Genetic factors associated with carbamazepine-induced DHRs**

Ethnicity	No. Positive for Target Genotype/ Total No.		Odds Ratio (95% CI)
	Case	Control	
HLA-B*1502			
Whites			
Alfirevic et al, ²⁸ 2006	0/2	0/43	NA
Lonjou et al, ²⁹ 2008	4/12	1/1290	644.50 (64.69–6431.36)
Han-Chinese			
Hung et al, ¹⁶ 2006	59/60	6/144	1357.00 (159.84–11,520.40)
Shi et al, ¹⁹ 2012	13/18	12/93	17.55 (5.31–58.06)
Wu et al, ²⁰ 2010	8/8	4/50	114.83 (6.25–2110.92)
Chang et al, ²³ 2011	12/16	47/300	16.15 (4.99–52.22)
Thai			
Locharernkul et al, ²¹ 2008	6/6	8/42	52.76 (2.70–1031.31)
Tassaneeyakul et al, ²² 2010	37/42	5/42	54.76 (14.62–205.13)
Korean			
Kim et al, ²⁶ 2011	1/7	2/485	40.25 (3.20–265.09)
Malaysian			
Then et al, ²⁴ 2011	6/6	0/8	221.00 (3.85–12,694.65)
Chang et al, ²³ 2011	12/16	47/300	16.15 (4.57–62.4)
Japanese			
Kashiwagi et al, ²⁷ 2008	0/2	1/371	49.40 (1.59–1531.08)
Indian			
Mehta et al, ²⁵ 2009	6/8	0/10	54.60 (2.25–1326.20)
HLA-A*3101			
Han-Chinese			
Hung et al, ¹⁶ 2006	8/31 ^a	4/144	12.17 (3.6–41.2)
Japanese			
Ozeki et al, ³⁰ 2011	37/61	47/376	9.5 (5.6–16.3)
Korean			
Kim et al, ²⁶ 2011	13/24	50/485	10.3 (4.4–24.2)
Whites			
McCormack et al, ⁴⁷ 2011	38/145	10/257	9.12 (4.03–20.65)

Abbreviation: NA, not applicable.

^a Subjects with maculopapular exanthema and DIHS-DRESS.

extended cohorts of Han Chinese^{16–20} and other Asian populations (including Thai,^{21,22} Malaysian,^{23,24} and Indian²⁵ groups). This has led the Food and Drug Administration to recommend screening HLA-B*1502 allele before starting CBZ treatment in individuals from genetically at-risk populations. However, the strong association was not replicated in other populations, including Korean, Japanese, and whites.^{26–29} By contrast, HLA-A*3101 was reported to be associated with CBZ-induced hypersensitivity in populations with a low frequency of HLA-B*1502.^{26,28,30} A recent study suggested that HLA-B*1502 represents a biomarker to predict the involvement of skin detachment in subjects with CBZ-induced SJS-TEN; however, HLA-A*3101 was related to CBZ-induced nonblistering hypersensitivity reactions, such as maculopapular exanthema (MPE) and DRESS.^{16,31} Ethnicity seems to play an important role in the association between HLA markers and AED DHRs. Studies in white populations show that the overall rate of CBZ-related SJS-TEN is very low and estimated at 1 to 6 per 10,000 newly exposed patients. In some Asian populations, HLA-B*1502 was also

observed in patients with DHRs to other AEDs such as LTG and PHT.²¹ A potential protective role of HLA-B*0702 was suggested in subjects with CBZ-induced SCARs.²⁸ A few studies suggested other potential genetic markers associated with AED DHR. Three single nucleotide polymorphisms of the heat shock protein-70 gene cluster in white patients with CBZ-induced SCARs.^{28,32} A polymorphism in the promoter region of the tumor necrosis factor α gene is also suggested as a predisposing factor for CBZ DHR.³³

Age

Drug metabolism is usually age-dependent and an increase in reactive metabolites may result in increased susceptibility to DHRs in children compared with adults, all drugs included.³⁴ Messenheimer and colleagues³⁵ reported that LTG-induced rashes are more common in children than in adults. The incidence of SJS in patients with LTG has also been estimated to be 10 times higher in children. The occurrence of DHRs resulting in discontinuation of the offending drugs tends to be more frequent in elderly patients. Various factors, such as age-related pharmacokinetic changes, altered homeostatic mechanisms, and combined medications and diseases, affect the prevalence and severity of AED DHRs.³ Children younger than age 12 years and adults older than age 64 years have higher risks for SCAR.¹¹

Drug-Related Factors

A recent multivariate analysis suggested that a history of rash with an AED was the strongest predictor of LTG-induced rash with an odds ratio of 3.62.³⁶ Concurrent medications can affect the susceptibility to developing allergic DHRs. A combination of valproate with LTG (particularly in patients taking a regular starting dose of LTG) has been reported to increase the risk of LTG-induced DHR.³⁷ In addition, the prevalence of AED DHRs increased five times in patients with a history of AED-induced eruption.⁸ Cutaneous hypersensitivity reactions are more frequent in adults with PHT, LTG, and CBZ, and less common (<1%) with other AEDs.³⁸

Disease-Related Factors

Immunologic disorders, such as systemic lupus erythematosus, corticosteroid treatment, and a family history of severe skin eruptions, are risk factors for AED DHRs.³⁹ Causality has not been conclusively proven. However, reactivation of human herpes viruses (HHVs) 6 and 7, cytomegalovirus, and Epstein-Barr virus may occur in association with DIHS-DRESS.^{40,41} Some patients with CBZ-induced DRESS had high levels of anti-HHV-6 antibodies and HHV-6 DNA copies in their sera.⁴² **Box 2** is a list of potential risk factors for antiepileptic drug hypersensitivity.

Box 2

Potential risk factors for antiepileptic drug hypersensitivity

Previous history of DHRs to other AEDs

Family history of AED DHR

Younger or elderly patients

Presence of viral infections (HHV-6, HHV-7, cytomegalovirus, Epstein-Barr virus)

Head injury

HLA-B*1502 Han Chinese and Southeast Asian carriers

HLA-A*3101 European and North Asian carriers

PATHOGENESIS

The pathogenesis of AED DHRs seems to be multifactorial. There has been significant evidence for immunologic mechanisms. A sensitization period of at least 7 to 10 days is required in patients with an AED DHR, resulting in a latent period before onset of symptoms and signs of DHR. Treatment dose of AEDs is not related to the onset and severity of DHRs. Immediate type I and immune complex-mediated type III hypersensitivity reactions are less frequently associated with AEDs. Instead, most DHRs to AEDs are mediated by nonimmediate (delayed) type IV reactions in which a specific HLA allele can activate drug-specific T cells with the offending AED. HLA molecules present endogenous or processed exogenous antigens to T cells that induce an adaptive immune response. The T-cell receptor (TCR) on the effector cells recognize the complex with drug-peptide and specific HLA molecules on the antigen-presenting cell, leading to the release of immune mediators, which then initiate an AED DHR.^{39,43–45}

Histopathological and immunologic findings suggest that AED DHRs are mainly mediated by adaptive immunity that involves major histocompatibility-restricted drug presentation, activation, and the clonal expansion of effector T cells.⁴³ CBZ and its reactive metabolites have been shown to directly activate T cells, confirming the hypothesis of direct pharmacologic interaction of drugs or metabolites with immune receptors.⁴⁵ In addition, the activated T cells from patients with CBZ-induced SJS released more than five times higher levels of interferon- γ and granulysin on CBZ stimulation compared with controls treated with gabapentin.⁴³ CBZ is metabolized as 30 metabolites in the human liver. A previous *ex vivo* experiment revealed that a high concentration of acridine (a CBZ metabolite) could trigger IL-5 production in T cells of susceptible individuals with a reduced threshold for secretion, such as individuals following a viral infection or with altered drug metabolism due to concurrent medications.⁴⁶ An altered balance between drug bioactivation and detoxification pathways may elevate levels of an AED or its reactive metabolites that bind irreversibly to cellular proteins and present to the immune system in the form of drug-modified proteins.³

Recent advances in pharmacogenomics studies demonstrate a strong genetic association between HLAs and specific drug-induced SCARs. A strong association between HLA-B*1502 and CBZ-induced SJS-TEN has been proven in the Han Chinese and Southeast Asian countries such as Hong Kong, Singapore, Thailand, Malaysia, and India.^{15–25} However, not all carriers of HLA-B*1502 have SJS when exposed to CBZ as described above. Ko and colleagues⁴³ identified a specific clonotype of TCR shared by patients with CBZ-induced SJS-TEN undetected in tolerant patients. They emphasized that CBZ-specific HLA-B*1502-restricted cytotoxic T-lymphocytes shared common TCR clonotypes, recognized CBZ or peptide-HLA B*1502 complexes, and induced SJS-TEN.⁴³ A recent genome-wide analyses reported that HLA-A*3101 was significantly associated with CBZ-induced DHRs in Korean, Japanese, and European populations.^{26,30,47} A relationship between HLA genotype and clinical phenotype of CBZ-induced DHRs determined by the extent of skin detachment was also demonstrated. The HLA-B*1502 allele showed increased sensitivity and a relative risk for CBZ-induced SJS-TEN with more extensive skin detachment, with no association in less severe reactions without detachment, such as MPE and DRESS in Han Chinese populations.^{16,31}

CLINICAL FEATURES

AED DHRs may present as mild cutaneous eruptions,^{8,48} such as MPE, erythema multiforme, and fixed drug eruptions, or as SCAR.⁴⁹ SCAR manifestations include

SJS-TEN, DIHS-DRESS,^{50,51} AGEP,⁵² and adverse reactions with overlapping clinical features.⁵³ The aromatic AEDs PHT, phenobarbitone, CBZ, and LTG are all classified as high-risk drugs^{38,54} with a predisposition to development of SCARs following long latent periods of up to 2 to 6 weeks from initiation of the drug. They may also be a cause of organ-specific allergic DHRs, such as leukocytosis, hepatitis,⁵⁵ acute tubulointerstitial nephritis⁵⁶ or acute kidney injury, myocarditis,⁵⁷ and thyroiditis.⁵⁸

DIAGNOSIS

Because nonimmediate DHRs to AEDs are more common than immediate reactions, skin patch tests have shown to be useful in the diagnosis of AED DHRs and are safe.^{59,60} **Box 3** presents common patch test concentrations for AEDs. The positive predictive value of tests under optimal conditions are reported to be as high as 80% to 90%, depending on the drug tested, with positive tests being drug-specific (ie, CBZ and PHT) and reaction-specific (ie, DRESS). Intradermal tests with delayed readings at 48 hours or 72 hours are used in lieu of patch tests in certain centers worldwide. However, the sensitivity, specificity and predictive values to diagnose nonimmediate DHRs to AEDs have not been well studied.

In vitro tests, such as the lymphocyte transformation test (LTT) and the lymphocyte toxicity assay (LTA), are more commonly used in research centers in view of technical demands to establish and interpret these tests. The sensitivity of the LTT and the LTA are around 70% and 90%, respectively, for AEDs. In addition, the positive and negative predictive values of the tests in highly imputable cases are high.⁶¹ Drug provocation tests should only be carried out in cases in which the history is not suggestive of AED DHRs, in-vivo or in-vitro tests are not conclusive or not available, and where the index reaction was not SCAR or an immunobullous reaction. The benefits of reaching a diagnosis of AED DHR must be carefully weighed against the risks of provoking a DHR during drug-provocation testing.⁶²

Although pharmacogenetic testing for the HLA-B*1502 allele before the initiation of CBZ in ethnic Asians has become the standard of care in Hong Kong and Taiwan, and is recommended in Singapore, it remains inconclusive whether this is cost-effective to prevent SJS-TEN.⁶³

MANAGEMENT

When AED DHR is suspected, the suspected AED should be stopped immediately. Mild cutaneous eruptions can be symptomatically treated and usually resolve with few sequelae.

Treatment modalities for SJS-TEN, including fluid replacement, maintenance of thermoregulation, dressings and wound debridement, ophthalmologic treatment, nutrition, and prevention and treatment of infection, apply to many different

Box 3
Common patch test concentrations for AEDs

Drug Name	Concentration (weight/volume percentage) (%)	Vehicle
Carbamazepine	1, 10	Petrolatum
Phenytoin	5, 10	Petrolatum
Lamotrigine	10, 50	Petrolatum
Phenobarbital	5, 10	Petrolatum

drugs and are not specific to AEDs. Despite on-going controversy about to whether high-dose intravenous immunoglobulins (IVIGs) at a dose of 2 g/kg reduces mortality in TEN,⁶⁴ up to 50% of practitioners worldwide continue to use this as the most common form of immunomodulatory therapy for TEN.⁶⁵ The evidence for IVIGs has been confounded by data predominantly from retrospective case series with variable inclusion criteria, high-risk and low-risk subjects, and subjects with TEN comprising those with SJS-TEN overlap as well. A recent systematic review and meta-analysis of the literature did not indicate any clinical benefit of IVIGs in children and adults.⁶⁶

There is renewed interest in the use of the calcineurin inhibitor, cyclosporin,^{67,68} which is the second most commonly used treatment of TEN in a worldwide survey.⁶⁴ Development of acute kidney injury due to TEN, hypovolemia, or sepsis often precludes the initiation or dose optimization of cyclosporin.

The use of systemic corticosteroids in SJS-TEN was evaluated in a case-control study based on data collected from EuroSCAR and RegiSCAR studies.⁶⁹ The previous use of corticosteroids prolonged the period of disease progression by 2.2 days (95% CI 1.1–3.2) with no influence on disease severity or mortality and delayed time to onset of SJS-TEN with exposure to high-risk drugs by 7.1 days (CI –0.2–14.5). Although there have been several case series and case reports (of which one showed histologic improvement of epidermal necrolysis on serial skin biopsies),⁷⁰ there are no controlled studies on the use of systemic corticosteroids in TEN. Although a tapering course of systemic corticosteroids is often used in the treatment of SJS⁷¹ and DIHS,⁷² there have been no controlled studies supporting this. Certain groups have recommended the use of combinations of a prolonged course of high-dose corticosteroids, IVIGs, and antivirals such as valganciclovir (if viral reactivation is confirmed) in the treatment of severe, life-threatening, or refractory visceral involvement in DIHS-DRESS.⁷³ AGEP is usually self-limiting, although oral corticosteroids may be useful to hasten recovery in some prolonged cases.⁷⁴

SUMMARY AND FUTURE DIRECTION

AEDs commonly induce DHRs and sometimes result in fatal outcomes such as SCARs. CBZ, PHT, and LTG are recognized as the major culprits of AED-induced DHRs. Two HLA alleles have been suggested as potential genetic markers for CBZ DHRs in various populations: HLA-B*1502 for Han Chinese and South Asian populations, as well as HLA-A*3101 allele in European and North Asian populations. Clinical predictors, such as a history of DHRs to aromatic AEDs, family history of DHR, age, and concurrent viral infections, can be used by physicians to minimize adverse reactions to an AED. Close monitoring during the initial latent period following AED initiation should also be observed. Further investigation to understand the pathogenic mechanisms (especially in aspects of genetics and immunologic mechanisms) will provide relevant in vivo and vitro testing and new therapeutic strategies for AED DHRs.

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