

Hypersensitivity Reactions to Antiepileptic Drugs in Children: Epidemiologic, Pathogenetic, Clinical, and Diagnostic Aspects



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Epilepsy affects approximately 10 million children globally. Antiepileptic drugs (AEDs) are among the most frequent causes of drug hypersensitivity reactions (DHRs), especially severe ones. However, systematic studies about AED hypersensitivity among children are very rare. In this review, we aimed to gather all relevant and important data about different aspects of DHRs to AEDs in children by conducting a PubMed search including English-language studies published between January 1990 and June 2017. In these studies, aromatic AEDs were mostly incriminated in DHRs, but still being dominantly prescribed in both developed and developing countries. Although newer AEDs were increasingly prescribed owing to their presumed low toxicity profile, surveillance of DHRs is strongly recommended because case reports about severe reactions were recently reported. The pathogenesis seemed to be multifactorial including metabolic, genetic, and immunologic factors. Recent pharmacogenomic studies demonstrated strong genetic associations between some human leucocyte antigens and/or polymorphisms of AED metabolic enzymes and AED-induced DHRs among both adults and children. Young children, concurrent medications, a high starting dose and rapid dose escalation, and some genetic markers are important risk factors for AED-induced hypersensitivity. There were a very limited number of studies in the pediatric population evaluating the efficacy of different available diagnostic tools, such as intradermal, patch, and drug provocation tests. Data including mostly adult patients showed that patch tests had relatively high diagnostic value to identify the culprit with a positivity rate that ranged between 19.7% and 100% in delayed reactions to AEDs. Clinical cross-reactivity rates of 15% to 70% have been reported mainly between aromatic AEDs. In selected cases, where there is no other option, desensitization can be considered, although experience in children remained limited. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1879-91)

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Epilepsy is one of the major neurologic problems facing both developing and developed countries. Fifty million people have epilepsy globally, of whom 20% are children, affecting an estimated 10.5 million children younger than age 15.¹ Owing to higher rates of hereditary, infectious, and hypoxic central nervous system disorders, the problem is more pronounced in developing countries, responsible for 80% of the 3.5 million new cases that are identified each year.^{1,2} Optimal treatment of epilepsy requires correct recognition of the type of seizures, selecting the most appropriate antiepileptic drugs (AEDs), and posology that may greatly improve safety and tolerability.^{3,4}

AEDs are classified as aromatic if their chemical structure contained at least 1 aromatic ring, namely, phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine (LTG), felbamate (FBM), zonisamide, and primidone⁵ (Figure 1). All other AEDs such as valproic acid (VPA), ethosuximide, gabapentin (GBP), levetiracetam (LEV), pregabalin, topiramate (TPM), clobazam (CLB), and vigabatrin (VGB) are classified as nonaromatic AEDs. Conventional AEDs such as PHT, PB, CBZ, and VPA are still commonly used among all age groups because of their efficacy and low cost, despite high toxicity and hypersensitivity potential.³⁻⁵ Although newer AEDs are increasingly prescribed among children owing to their presumed low toxicity profile, surveillance of adverse reactions is strongly recommended, as the safety of these drugs has not been established in the long term.⁶⁻⁸ The prescription rates of AEDs and patterns of AED choice in children and adolescents show substantial variations between countries and also changing trends over years.⁸⁻¹² The prevalence of AED use among the pediatric population varied between 2.1 and 4.11 per 1000 children in the last decade.⁹⁻¹³

In this review, we aimed to gather all relevant and important data regarding the epidemiologic, pathogenetic, clinical, and diagnostic aspects and management of hypersensitivity reactions to AEDs in epileptic children who present a global group of millions of new cases that are identified each year.^{1,2} A PubMed search was conducted with the purpose of identifying English-language studies published between January 1990 and December 2017 that reported about AED-related hypersensitivity or idiosyncratic reactions occurring in children.

EPIDEMIOLOGY

Adverse drug reactions (ADRs) are commonly experienced by approximately one-third to more than half of adults and children receiving an AED treatment.¹⁴⁻¹⁸ Although AEDs are among the

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Abbreviations used

ADR-	Adverse drug reaction
AED-	Antiepileptic drug
AGEP-	Acute generalized exanthematous pustulosis
AHS-	Anticonvulsant hypersensitivity syndrome
CBZ-	Carbamazepine
CLB-	Clobazam
CYP-450-	Cytochrome P-450
DHR-	Drug hypersensitivity reaction
DILI-	Drug-induced liver injury
DPT-	Drug provocation test
DRESS-	Drug reaction with eosinophilia and systemic symptoms
EPH-	Epoxide hydrolase
FBM-	Felbamate
GBP-	Gabapentin
HHV-6-	Human herpesvirus-6
HLA-	Human leucocyte antigen
HSR-	Hypersensitivity reaction
LEV-	Levetiracetam
LTG-	Lamotrigine
LTT-	Lymphocyte transformation test
MHC-	Major histocompatibility complex
MPE-	Maculopapular exanthem
OXC-	Oxcarbazepine
PB-	Phenobarbital
PET-	Petrolatum
PHT-	Phenytoin
SCAR-	Severe cutaneous adverse reaction
SJS-	Stevens-Johnson syndrome
TCR-	T-cell receptor
TEN-	Toxic epidermal necrolysis
TPM-	Topiramate
VGB-	Vigabatrin
VPA-	Valproic acid

most frequent causes of ADRs in children, these reactions are often mild and tolerable.¹⁶⁻¹⁸ However, more severe, sometimes fatal, reactions can also occur.^{14,16,18-20}

Most of the epidemiological and clinical studies on ADRs to AEDs lack a clear description and differentiation between type A (predictable, dose dependent, and pharmacologic associated) and type B reactions (unpredictable, not dose dependent, and idiosyncratic), which mostly include drug hypersensitivity reactions (DHR).^{21,22} DHRs with clearly defined immunologic (mostly IgE or T-cell mediated, or, rarely, IgG antibody, or immune complex-mediated reactions) mechanisms are referred to as drug allergy.²² In the literature relevant to AEDs, DHRs are mostly referred to as and collected under the heading of “idiosyncratic reactions” or “cutaneous adverse reactions” and isolated pediatric studies are rare.¹⁵⁻¹⁸ Moreover, because objective *in vivo* and *in vitro* testing are not generally performed, most of the reactions labeled as hypersensitivity or idiosyncrasy are not really confirmed.^{14,18,19}

Although DHRs only account for 10% to 30% of all ADRs in general, they are a major source of morbidity and mortality.^{20,21,23} AED-induced DHRs, which are reported to be more common in children, present with a variety of clinical manifestations ranging from benign skin rashes to severe and sometimes fatal reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) (or synonymous anticonvulsant hypersensitivity syndrome [AHS]/drug-induced hypersensitivity

syndrome), and rarely acute generalized exanthematous pustulosis (AGEP).^{14,16,23-25} Anticonvulsants were the leading cause of fatal reactions among children based on all reports received from 1964 until December 2000 by the UK Committee on Safety of Medicine.²⁰

Hypersensitivity reactions (HSRs) linked to the administration of AEDs in children was first reported in 1934 by Silber and Epstein.²⁶ They described it as a “nirvanol sickness,” a name given after administration of PHT that was used as a “nerve sedative” in Germany, and the authors reported the appearance of rash, fever, leukopenia, and eosinophilia in a group of children with chorea using PHT treatment.²⁶ Beginning from the early 1960 to 1970s, a substantial number of pediatric cases who showed a large spectrum of DHRs with the administration of antiepileptics were increasingly reported.²⁷⁻³⁰

The prevalence of HSRs to AEDs varies according to the populations enrolled, offending drugs, and study design. Systematic studies on AED-induced DHRs in children are rare and most reports include both children and adults.^{14,17-19,24} Epidemiologic and clinical analysis of DHRs in hospital-based series of pediatric patients from different countries showed that AEDs were frequently within the top 5 implicated drugs for the whole spectrum of clinical presentations and aromatic AEDs had 2 to 5 times higher rate of DHRs than new generation and/or nonaromatic AEDs in hospitalized and outpatient populations.^{29,30,31-35} Isolated cutaneous eruptions such as morbilliform rash and urticaria are the most common manifestation of AEDs and occur in 2% to 16% of individuals who receive them.^{23,30,34-36} Antiepileptics, particularly aromatic ones, are among the most common causes of severe cutaneous adverse reactions (SCARs) that include SJS, TEN, DRESS, and AGEP among children and adults.^{24,36-45} In a multicenter Turkish study evaluating SCARs in children, approximately one-third of the drugs that cause SJS/TEN and DRESS were AEDs.⁴³ Recent data from the United Kingdom showed that absolute risks for SJS/TEN were highest for PHT (45.86 cases/100,000 exposed), LTG (44.17 cases/100,000 exposed), and CBZ (20.38 cases/100,000 exposed) and lower for VPA and others in new users of AED therapy.⁴² Isolated pediatric data on the relation between drugs and SJS/TEN were investigated in a pooled analysis of 2 multicenter international case-control studies: the SCAR study and the multinational severe cutaneous adverse reaction study including subjects aged <15 years hospitalized for SJS/TEN.⁴⁶ The results showed that anti-infective sulfonamides and AEDs, namely PB, CBZ, and LTG, were the drugs most strongly associated with the risk of SJS and TEN in children. A multicenter Italian surveillance study of children hospitalized through the emergency departments for SJS showed that anticonvulsants presented the highest adjusted risk (adjusted odds ratio: 26.8) for the development of SJS among all other drugs and vaccines.²⁵

Aplastic anemia, drug-induced liver injury (DILI), and pancreatitis are rare and severe DHRs reported in adult and pediatric patients receiving AEDs, especially VPA and aromatic ones.⁴⁷⁻⁵² In an overall review of Vigibase reports, a disproportionately higher reporting frequency was noted for children compared with adults for VPA-induced aplastic anemia.⁵⁰ Idiosyncratic DILI is rare, with an incidence of approximately 19 per 100,000 treated individuals, and antibiotics, anticonvulsants, and antidepressant therapy remain the commonest causes.⁵¹ In one of the scarce reports on pediatric DILI, antituberculous drugs were the most common cause, followed by the AEDs, that

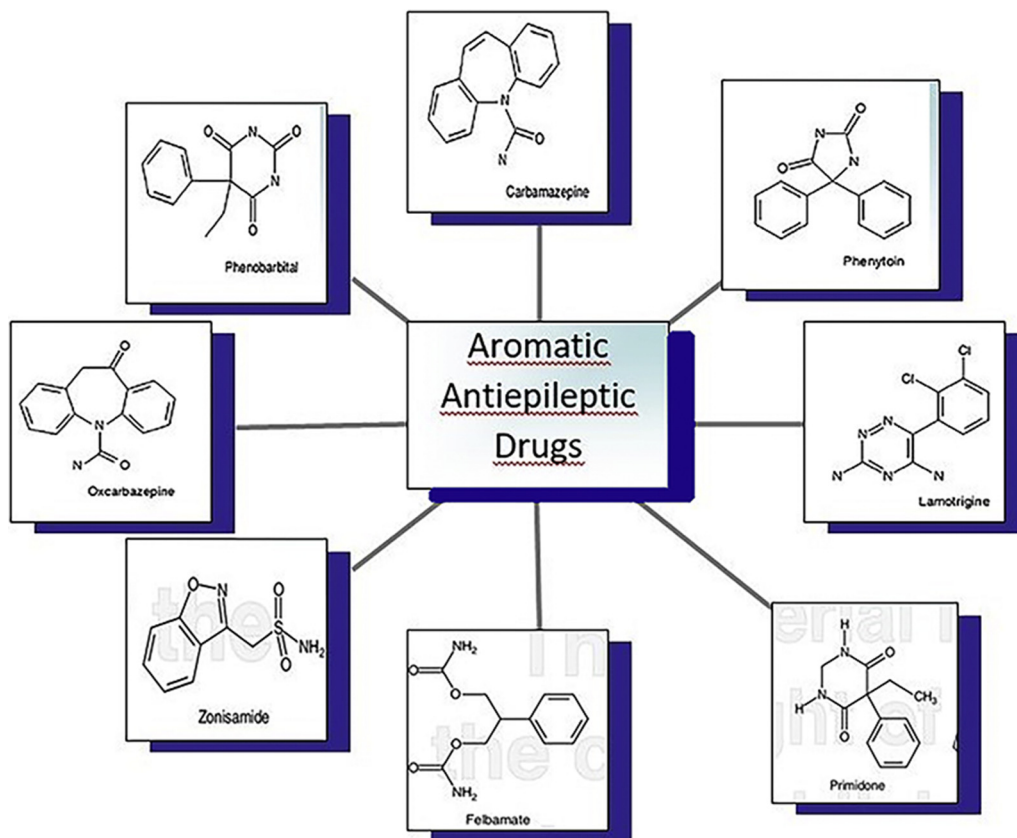


FIGURE 1. Aromatic antiepileptic drugs.

is, PHT and CBZ, in a series of 450 children with DILI.⁵² Levetiracetam is an increasingly used new nonaromatic AED and reported to have a better tolerability profile in general.^{7,8,14,53} However, recently there have been isolated case reports of LEV-induced rash, and also severe reactions, in children and adults.^{36,54-57}

PATHOGENESIS

The pathogenesis of HSRs to AEDs seems to be multifactorial including metabolic, genetic, and immunologic factors and has not been fully understood^{19,23,34,58,59} (Figure 2). Several models have previously been suggested to explain the nature of immune activation during AED-induced DHR. The first is the hapten/prohapten hypothesis, which proposes that the AED is oxidatively metabolized to reactive, potentially cytotoxic intermediate molecules capable of interacting covalently with cellular macromolecules, that is, they behave as hapten or prohaptens.^{59,60} These drug-modified proteins could then function as immunogens, with the potential to initiate antibody and/or cellular-mediated immune response against drug-modified or native proteins.⁵⁹ Immediate type I (eg, anaphylaxis, urticaria/angioedema), antibody-mediated type II (eg, cytopenias, aplastic anemia), and immune complex-mediated type III hypersensitivity (eg, serum sickness) reactions are less frequently associated with AEDs.^{19,23,34} Instead, most HSRs to AEDs are mediated by nonimmediate (delayed) type IV reactions (eg, maculopapular exanthem [MPE], DRESS, SJS/TEN, DILI) in which a specific

human leucocyte antigen (HLA) allele presents and activates drug-specific T cells.⁵⁸⁻⁶³ Besides the classical model of the antigen-presenting cell-T cell interaction, an alternative mechanism by which delayed hypersensitivity may occur is described by the so-called p-i concept, that is, pharmacological interaction with immune receptors.⁶⁴ According to this concept, drugs or metabolites can interact directly and noncovalently with the MHC and/or T-cell receptor inducing the formation of HLA, drug complexes that activate T-cell immune responses without requiring a specific peptide ligand.^{62,64} CBZ and its reactive metabolites have been shown to directly activate T cells, confirming the hypothesis of "p-i concept" for AED hypersensitivity.⁶⁵ A third mechanism includes the "altered peptide repertoire" hypothesis, which postulates that the drugs or its metabolites can bind noncovalently within the pocket of the peptide binding groove of certain HLA molecules, potentiating a new repertoire of endogenous self-peptides to be bound and presented.^{66,67} It was demonstrated that the binding of CBZ to HLA-B*15:02 alters the repertoire of presented self-peptides.⁶⁷

Immune-mediated reactions to AEDs are largely, but insufficiently, explained by the hapten/prohapten, "p-i concept," and "altered peptide repertoire" hypotheses. The recently proposed "danger hypothesis" is based on the requirement of costimulatory signals for the boosting of the immune response to a drug-derived antigen.^{61,68} The costimulatory "danger signals" that might result from chemical, physical, cellular, or viral stress interact with antigen-presenting cells to promote an adaptive immune response.^{61,68-70} It has been reported that severe

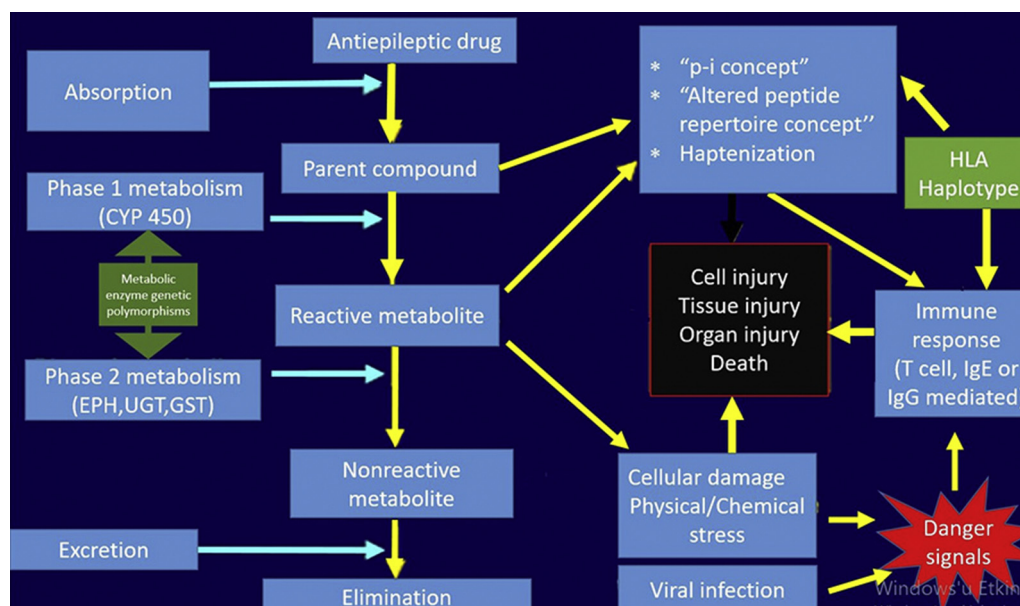


FIGURE 2. Possible role of metabolic, immunologic, and genetic factors in the pathogenesis of hypersensitivity reactions to antiepileptic drugs. Metabolism of antiepileptic drugs (AEDs) include phase 1 (bioactivation) and phase 2 (detoxification) reactions that may be affected by metabolic enzyme genetic polymorphisms. An altered balance between drug bioactivation and detoxification pathways may elevate levels of the reactive metabolites, which either cause direct cell damage or trigger an immune response with 3 pathways. The classical pathway involves covalent binding to a macromolecule (haptenization) and antigen processing and presentation. Alternative pathways include “p-i concept” and “altered peptide repertoire” hypotheses that propose noncovalent antigen interaction with the major histocompatibility complex (MHC) and/or T-cell receptor activating T cell immune response, and binding of drug molecules noncovalently within the pocket of the peptide binding groove of certain human leucocyte antigen (HLA) molecules, potentiating a new repertoire of endogenous self-peptides, respectively. Certain HLA haplotypes encoding MHC molecules may play an important role in the presentation or activation of immune response to a particular AED in the context of these hypotheses. Additional “danger signals” originating from stress induced by viral infections, cellular insult, and toxic intermediates may provide the co-stimulatory signals for the boosting of the immune response to AED-derived antigen. *CYP*, Cytochrome; *EPH*, epoxide hydrolase, *GST*, glutathione S-transferase; *HLA*, human leucocyte antigen; *p-i*, pharmacological interaction with immune receptors; *UGT*, uridine glucuronosyltransferase.

hypersensitivity to CBZ may be associated with a genetic polymorphism of the promoter region of the proinflammatory cytokine tumor necrosis factor- α and with the heat shock protein-70 gene cluster, which may be involved in reactions to stress.⁷¹ Active viral infections, which are reported in up to 76% of patients with DRESS, can be boosting stimuli, in accordance with the “danger hypothesis.”⁷²⁻⁷⁴ However, it is not completely clear whether Humanherpesvirus-6 (HHV-6) and other viral reactivation are a consequence of a strong immune modulation during DRESS or a cofactor that favors the development of this syndrome.⁷⁴⁻⁷⁷

Alterations in drug metabolism may also play an important role in HSRs to AEDs.^{60,77-79} The cytochrome P-450 (CYP-450) enzymes such as CYP2C19, CYP2C9, and CYP3A5 are the main enzymes responsible for metabolizing the aromatic AEDs to reactive metabolites such as arene oxide, whereas the epoxide hydrolase (EPH), glutathione S-transferase, and uridine glucuronosyltransferase enzyme systems are responsible for detoxifying these metabolites.^{58,80,81} An altered balance between drug bioactivation and detoxification pathways may elevate levels of reactive metabolites that may directly cause cell death, or bind irreversibly to cellular proteins and are presented to the immune system in the form of drug-modified proteins.^{60,80-83} As drug metabolic profiles are often determined by variability in the genes coding for drug-metabolizing enzymes, it is reasonable that

pharmacogenetic variations in drug metabolism may result in an altered drug metabolism, generation of reactive drug metabolites, and hence DHRs.⁸⁴⁻⁸⁷ Although earlier studies could not find potential genetic defects related to EPH enzyme,⁸² a recent study found a significant association between epoxide hydrolase 1 gene c.337T>C polymorphisms and the development of CBZ-SJS/TEN in patients of Chinese Han ethnicity.⁸⁴ In the last 10 years, a significant number of studies have revealed significant associations between polymorphisms in drug metabolism of AEDs and certain types of DHRs.⁸⁸⁻⁹³ A recent genome-wide association study in Taiwanese, Japanese, and Malaysian patients showed a strong association between phenytoin-induced SCAR and CYP2C9*3, an allelic variant that reduces CYP2C9 enzymatic activity by approximately 90%.⁸⁹ Pediatric genetic studies related to aromatic AED metabolism showed significant associations between PHT-induced SCAR and CYP2C9*3 and PB-induced SCAR and CYP2C19*2 variants in Thai children.^{91,92}

The biological function of HLA is to present antigens to the T-cell receptor (TCR) and then elicit specific T-cell-dependent immune response.^{62,64,66,77,94} Recent pharmacogenomic studies demonstrated strong genetic associations between certain HLAs and AED-induced DHRs, especially SCARs.⁹⁵⁻¹⁰⁶ A very strong association between HLA-B*15:02 and CBZ-induced SJS-TEN has been proven in the Han Chinese and Southeast Asian populations, but not in Caucasians and Japanese.⁹⁷⁻¹⁰⁰ It has been

also shown that HLA-B*15:02 was a common risk allele for SJS/TEN induced by most of aromatic AEDs in Han Chinese, and it is recommended that aromatic AEDs, including CBZ, OXC, and PHT, should be avoided in the HLA-B*15:02 carrier and caution should be applied also for LTG.⁹⁶ Another remarkable genome-wide analysis reported that HLA-A*31:01 was significantly associated with CBZ-induced DHRs in Korean, Japanese, and European populations.¹⁰³⁻¹⁰⁵ The exact mechanism of how carrying HLA-B*15:02 or HLA-A*31:01 results in an increased risk of AED hypersensitivity is not clear. It is thought that the MHC molecules encoded by these particular HLA alleles interact with the AED or a AED-derived molecule in a way that they are recognized by T cells as “nonself,” which triggers an immune reaction.^{74,77,94} Ko et al¹⁰¹ found that CBZ-specific HLA-B*15:02-restricted cytotoxic T-lymphocytes shared common TCR clonotypes, recognized CBZ or peptide-HLA B*15:02 complexes, and induced SJS-TEN. Combined screening for CYP2C9 variants and HLA-B*15:02 carriage improved the sensitivity but decreased the specificity for phenytoin-induced SJS/TEN, when compared with screening for CYP2C9 variant alone.⁹⁰ These findings add to a growing number of observations showing that multiple processes including pharmacological and immunological mechanisms contribute to DHRs that may be mediated by the parent drug or metabolites. One of the most recent pharmacogenomic studies about AED-induced DHRs revealed HLA-A*24:02 as a shared risk factor for SJS/TEN induced by the aromatic AEDs in a southern Han Chinese population.¹⁰⁶ There are few studies that searched for the association between certain HLA alleles and/or CYP-450 isoforms and AED-induced HSRs only among children. An association between PB hypersensitivity and HLA-A*01:01 and HLA-B*13:01 was shown in Thai children.¹⁰⁷ Other studies revealed that HLA-B*15:02 positivity increased the risk of CBZ-induced SCAR in Singapore children of Chinese and Malay ethnicity, but this haplotype was not correlated with AED-induced SCAR in Iranian children.^{108,109} A pediatric multicenter consortium study including patients from North America with a diverse ethnic background showed that HLA-A*31:01 was significantly associated with CBZ-induced DRESS and MPE but not with CBZ-induced SJS. Conversely, HLA-B*15:02 was associated with CBZ-induced SJS but not DRESS or MPE.¹¹⁰

Some idiosyncratic reactions appear to be caused by a direct cytotoxic effect of the drug or its metabolites, without pathogenetic involvement of the immune system.⁶⁰ As far as AEDs are concerned, the best example of such reactions is probably VPA-induced hepatotoxicity.^{50,51,111}

RISK FACTORS

The incidence and severity of idiosyncratic or HSRs to AEDs may be affected by various factors. Identifying susceptible individuals and risk factors, and close clinical monitoring during the latent period are key to the prevention of these reactions.^{3,14,15,19}

Age and sex

Age-related differences in drug metabolism, particularly the reduction in glucuronide conjugation in young infants, and the faster rates of CYP-mediated reactions in infants and children compared with adults may result in increased susceptibility to DHRs in young children compared with older children and

adults.^{23,31,79,112,113} The best example of a DHR that occurs more frequently in children than in adults is LTG-induced mild and severe rashes that are seen 10 times higher than adults.¹¹⁴⁻¹¹⁶ Children younger than age 5 years have 3 to 5 times higher risks for SCAR and other rash related to AEDs.^{23,117,118} Young age is also a major risk factor for VPA-induced toxic hepatitis, for which the highest risk was reported to be in children younger than 2 to 6 years of age in different studies.^{50-52,113} A large-scale population study showed that AED-related skin reactions developed significantly more often in females than in males.³⁵

Viral infections

Viral infections can be another cofactor and probably play an important role in AED-induced DRESS because reactivation of latent HHV infections are frequently detected.^{68,72,73,76,77} However, it has been controversial whether the viral infection or reactivation is a triggering cofactor, or a result of hypersensitivity to the drug itself.^{76,77} It is also uncertain whether the commonly encountered viral infections of childhood play a role or trigger HSRs to AEDs in children.

Concomitant diseases associated with epilepsy

HSRs to aromatic AEDs are more frequently observed in patients with other immune system disorders, systemic lupus erythematosus, infectious diseases, and in those who are under treatment with corticosteroids.^{3-5,14,23} It has been shown that the binding of AEDs to proteins is decreased in patients with head trauma, and therefore, head trauma may be a potential risk factor for AED HSRs.¹¹⁹ However, causalities have not been conclusively proven for these risk factors. Neurologic disabilities and several metabolic disorders were found as significant risk factors for severe VPA-induced hepatotoxicity.^{14,50,51}

Drug structure, dose, and concomitant drugs

The presence of an aromatic ring is an important risk factor for “idiosyncratic” or hypersensitivity reactions.^{23,31,34-36,118} In addition, it has been reported that a previous AED-related skin reaction appears to be a significant risk factor for the occurrence of HSR to a previously tolerated other AED.^{36,79,120} Among drug-related variables, a high starting dose and rapid dose escalation were identified as risk factors, especially for LTG, particularly when administered concurrent with VPA, and also for CBZ and PHT.^{4,15,113,116,121-123} However, a pediatric study showed that HLA-B*15:02 positivity increased the risk of CBZ-induced SCAR in Asian children at relatively low doses.¹⁰⁸

Concurrent medications, including both AEDs and non-AEDs such as antifungals and macrolides, can affect the susceptibility to developing HSRs to AEDs as a result of CYP450 metabolism competition and protein binding.^{3,5,14,15,18,19,31,37,60} In general, enzyme inducers decrease the serum concentrations of other drugs metabolized by the system and enzyme inhibitors have the opposite effect.^{3,5,7,15,114} Overall, conventional AEDs such as CBZ, PB, PHT, and VPA are generally more prone to drug interactions, whereas newer AEDs have less potential due to minimal or null binding to blood albumin (eg, eslicarbazepine acetate [ESL], FBM, GBP, lacosamide [LCS], LEV, rufinamide [RUF], TPM, and vigabatrin [GVG]), and their primary renal excretion or metabolism by non-CYP enzymes.^{3,5,7,15,79,80} Coadministration of inhibitors of enzyme systems such as VPA, OXC, TPM, and FBM may be particularly likely to result in increased levels of the parent

molecule or toxic intermediate metabolites of the other first line AEDs such as PHT and PB.^{5,15,95,114} A combination of VPA with LTG (particularly in patients taking a regular starting dose of LTG) has been consistently reported to increase the risk of LTG-induced DHR.^{33,37,115}

Genetic factors

Identical twins and siblings may experience similar idiosyncratic reactions to AEDs.^{124,125}

As mentioned above in the Pathogenesis section in detail, pharmacogenomic studies revealed many associations between genetic variations in drug metabolism and HLA genotypes and AED-induced DHRs in the last decade.^{96-110,126} The most important HLA-AED hypersensitivity associations revealed up to now are as follows:

- A very strong association between HLA-B*15:02 and CBZ-induced SJS/TEN in the Han Chinese and Southeast Asian populations.^{97-100,126}
- HLA-B*15:02 as a common risk allele for aromatic AED-induced SJS/TEN in Han Chinese.⁹⁶
- HLA-B*15:02 and OXC-induced SJS/TEN in Asian populations (Chinese and Thai).¹⁰²
- HLA-A*31:01 and CBZ-induced DHRs in Korean, Japanese, and European populations.¹⁰³⁻¹⁰⁵
- HLA-A*24:02 as a shared risk factor for SJS/TEN induced by the aromatic AEDs in southern Han Chinese.¹⁰⁶

Few pediatric studies that searched for the significant associations between certain HLA alleles and AED-induced DHRs among children revealed:

- HLA-A*01:01 and HLA-B*13:01 and PB hypersensitivity in Thai children.¹⁰⁷
- HLA-B*15:02 and CBZ-induced SCAR in Singapore children of Chinese and Malay ethnicity.¹⁰⁸
- HLA-A*31:01 and CBZ-induced DRESS and MPE, and HLA-B*15:02 and CBZ-SJS in pediatric patients from North America with a diverse ethnic background.¹¹⁰

Also, in the last 10 years a significant number of studies have revealed significant associations between genetic polymorphisms in drug metabolism enzymes and certain types of DHRs induced by AEDs (mentioned in detail in the Pathogenesis section).⁸⁴⁻⁹³

CLINICAL FINDINGS

AEDs may cause a variety of DHRs from benign skin rashes to severe reactions such as SJS/TEN, DRESS, agranulocytosis, aplastic anemia, DILI, pancreatitis, and rarely AGEP.^{14,16,17,23,42,44} Isolated cutaneous eruptions, which include mostly MPE and more rarely urticaria/angioedema, are the most common manifestations of HSRs to AEDs.^{23,31,34-36} Drug-related morbilliform/maculopapular eruptions present as a spotty, nonconfluent, and nontender rash resembling viral infections; facial involvement is usually minor, there is no facial or neck edema, and pruritus is infrequent.^{19,23,36} IgE-mediated reactions such as urticaria, angioedema, and anaphylaxis are relatively rare when compared with T-cell-mediated reactions, but may infrequently occur with both conventional and new antiepileptics.^{56,127-131}

DRESS is a rare but potentially life-threatening DHR of which AEDs are among the most common causes.^{24,40,45,83,132,133} DRESS is reported rarely with VPA.¹³³ Although LEV is proposed to be a safer AED, pediatric and adult DRESS cases related to LEV use have been also reported.^{54,55,134,135} Important diagnostic criteria for DRESS are: (1) fever $\geq 38.5^{\circ}\text{C}$; (2) nonspecific skin rash, which often resolves with desquamation; (3) hematological abnormalities such as eosinophilia ($\geq 1.5 \times 10^9/\text{L}$) and/or the presence of atypical lymphocytes in peripheral blood; (4) systemic involvement such as lymphadenopathy, hepatitis, interstitial nephritis, carditis, and interstitial pneumonia; (5) resolution after more than 15 days.^{45,132} The Japanese definition of DRESS (synonymous AHS is more commonly used in Asia) also includes viral reactivation, the most prevalent being HHV-6 and other herpesviruses, as a criterion for diagnosis.^{73,76,136} Facial edema, which is a characteristic feature, frequently accompanies the rash, in addition to other symptoms and signs.^{25,40,45,132} There is a remarkably long latency period of 2 to 8 weeks between initiation of the drug and initial disease symptoms, and resolution is also gradual after drug withdrawal.^{24,40,45} In up to 20% of cases, the disease can persist for several months with a series of remissions and relapses.^{40,132,136-138} Exposure to drugs other than the culprit drug may result in neosensitization to these agents during the active phase of DRESS.^{75,139} It is important that clinicians, particularly pediatricians and pediatric neurologists, give close attention to the occurrence of DRESS during AED treatment.

SJS and TEN are among the most dangerous DHRs associated with high morbidity and mortality rates reaching 30% to 50% of victims.^{38,39,117} Although most pediatric cases were related to aromatic AEDs, case reports including SJS/TEN related to new generation AEDs such as LEV are present.^{57,134,140-143} SJS and TEN are considered to be clinically and immunopathogenetically the same syndrome representing different severities depending on the extension of skin detachment.^{38,39,142,144} SJS/TEN, which may develop 4 days to 4 weeks after initiation of the respective drug, is a systemic and severe DHR characterized by fever, malaise, cutaneous, and mucosal lesions of more than 1 anatomic site, commonly preceded by nonspecific prodromal symptoms lasting 1-7 days.^{25,32,39,44,140} Involvement of mucous membranes is manifested by purulent conjunctivitis and inflammation, erosions, ulcers, and crusts of other mucosal surfaces such as the mouth, nose, pharynx, respiratory and digestive tracts, and anogenital mucosa, which may result in potentially life-threatening complications.^{140,142,143,145} Skin lesions present as red macules and papules that coalesce to a generalized erythematous rash with atypical targetoid lesions, and progress to vesicles, bullae, and extended skin necrosis that detaches in large sheets.^{142,144,146} In atypical flat target lesions, there is no palpable edema, there are 2 concentric zones, and often there is a central blister within the target-like erythema.^{142,144,146} When the leading cutaneous finding is erythema, the Nikolsky sign positivity may help diagnosis, although it is not exclusive of SJS/TEN.¹⁴⁵ Recovery may be slow, taking several weeks and long-term sequelae are frequently seen.^{140,143,144}

Although there have been case reports of AGEP cases caused by AEDs, these drugs are not included among the most common

causes of this syndrome.^{35,147-149} The clinical picture of AGEF is characterized by fever, pinhead-sized nonfollicular sterile pustules on erythematous skin lesions initially arising in the face and intertriginous areas, leukocytosis, and rare organ involvement.^{32,62,146,147}

Aplastic anemia is the most frequent and serious hematological reaction reported with AEDs, mostly with FBM but also other aromatic AEDs.^{47-50,150-152} More rarely, selective suppression of bone marrow cells may also lead to agranulocytosis and pure cell aplasia in AED users.^{47,150} Sporadic pediatric cases of thrombocytopenia, probably immune mediated, have also been described among conventional, but also new AED users.^{47,150,153,154}

AEDs, especially VPA and FBM, have been recognized as important causes of immune-mediated and idiosyncratic DILI among children and adults.^{50-52,119,155,156} The highest risk (1:500) of fatal VPA-induced hepatotoxicity is in children younger than 6 years on polytherapy, particularly in the presence of an inborn metabolic disorder.^{50,156,157} Hepatitis may be one of the symptoms of DRESS or occur in isolation, especially if caused by immune-mediated mechanisms or direct cytotoxic damage.^{50,111} Hepatotoxicity from AEDs typically develops 1 to 16 weeks (usually 4 weeks) after treatment initiation.^{155,156} Patients may have asymptomatic elevation of liver function tests or have symptoms ranging from nonspecific nausea, vomiting, anorexia, to specific symptoms of right upper quadrant pain, skin rashes, itching, jaundice, ascites, and encephalopathy.^{50,51,119,156} Immune-mediated DILI have a milder course and a better survival, particularly in children, and are often accompanied by hypersensitivity features such as skin rashes, eosinophilia, or lymphadenopathy, which may aid in the differentiation of hypersensitivity DILI from the metabolic idiosyncrasy variety.^{50,51,155,156} Failure to stop the drug with the onset of DILI often results in high morbidity, mortality, or chronicity.^{50,119,155,157}

Pancreatitis is a rare complication of VPA therapy, with a high mortality rate among children and adults.^{14,18,19,50,158,159} Occasional cases of pancreatitis have also been reported with other AEDs.^{16,23,26} Age less than 20 years, polytherapy, chronic encephalopathy, and hemodialysis are strong risk factors for VPA-associated pancreatitis.^{19,23,26,158}

DIAGNOSIS

The diagnosis of hypersensitivity to AEDs remains difficult due to the limited number of studies evaluating the efficacy of different available diagnostic tools, particularly in the pediatric population. IgE-mediated reactions such as urticaria, angioedema, and anaphylaxis are relatively rare when compared with T-cell-mediated reactions, but may infrequently occur with both conventional and new antiepileptics.^{23,31,34-36} In immediate-type reactions, skin prick and intradermal tests with immediate (20th minute) reading and, if negative, a drug provocation test (DPT) should be performed.^{21,160} However, nonirritating concentrations for prick and intradermal tests have not been evaluated or reported for AEDs.¹⁶⁰ Regarding nonimmediate hypersensitivity to AEDs, according to international guidelines, the diagnosis is mainly based on delayed-reading intradermal tests, patch tests, lymphocyte transformation tests (LTTs) and/or a DPT.^{21,160} Although there are limited data regarding the optimal concentration for patch tests, the maximum recommended

concentrations have been found to be 10% in petrolatum (PET) for pure substances and 30% in PET for commercialized forms of AEDs.^{161,162} In a limited number of studies, several patch test concentrations from 1% to 30% were used with different AEDs.^{31,163-165} It is recommended not to exceed 20% for CBZ and 30% for other AEDs.¹⁶² In patients with suspicion of severe nonimmediate drug allergy such as DRESS or SJS/TEN, it is recommended to start at a concentration of at least 1%.^{161,165} Because of the lack of confirmatory DPT in the majority of the published studies, the exact diagnostic value of skin tests and *in vitro* tests remains unknown. Indeed, only few studies including a limited number of patients investigated the diagnostic value of patch tests and/or LTTs in nonimmediate AEDs HSRs, mainly with CBZ.¹⁶⁶⁻¹⁷¹ Based on these data, it has been shown that the rate of positive patch tests ranges between 19.7% and 100%.^{31,166,170-175} Although drug patch tests were reported to be safe and with a relatively high diagnostic value to identify the culprit in AED-induced MPE and DRESS, the diagnostic value of patch tests for AED-induced SJS/TEN remains not well defined.¹⁶³⁻¹⁶⁵ However, in 1 study, 62.5% of the 16 CBZ-related SJS/TEN patients and 70% of the 10 CBZ-related DRESS patients of Asian ancestry had positive patch test reactions to 30% CBZ.¹⁶⁵ Skin tests are more often recommended in patients with a low suspicion, or to find safe alternatives in SCARs.^{174,176-178} In addition, the diagnostic value of patch tests varies according to the incriminated drug, with a reported higher sensitivity for CBZ, compared with PHT and PB.^{161,170,174,179} Of note, it has been suggested that patch testing with the incriminated drug as well as with its metabolites could increase the diagnostic value.^{166,171} However, these data need to be confirmed by further studies, particularly in the pediatric population.

Regarding *in vitro* tests, the performance of the LTT appears to be low and is poorly studied in the pediatric population.^{166,169,180,181} The tests should be ideally performed 6 to 8 weeks after the initial reaction due to a potential refractory period immediately after the reaction and the potential decrease of sensitivity over time.^{161,179,180} As mentioned above, genetic polymorphisms from HLA genes have been recently shown to be a powerful tool in predicting adverse reactions to some AEDs, particularly CBZ. Thus, a strong association between the HLA-B*15:02 allele and CBZ-induced SJS/TEN in patients of Asian ancestry has been shown.^{97-100,182,183} Cost-effectiveness analyses have demonstrated that this testing is useful in several Asian countries,¹⁸⁴ but also in other countries in patients of Asian descent before CBZ treatment.¹⁸⁵⁻¹⁸⁷ Screening for HLA-A*31:01 allele before administration of CBZ has also been proposed as a cost-effective measure in European countries, although no consensus has been reached.^{110,188} A diagnostic approach is recommended in Figure 3 that should be performed in case of a suspected AED allergy among children, because overdiagnosis is a common problem especially in this age group.^{21,29,31,168,176} (Figure 3).

MANAGEMENT

After the treatment of the reaction during the acute phase according to international recommendations, identification and elimination of the culprit drug remains the cornerstone of the management of children diagnosed with drug allergy. Then, the initial indication for AEDs should be questioned and

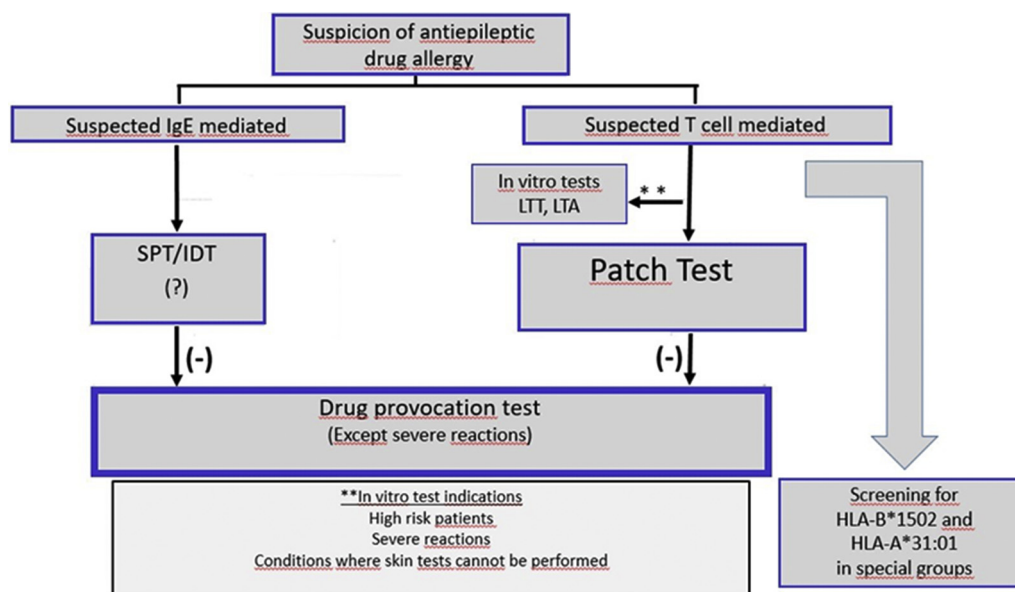


FIGURE 3. Approach to diagnosis in suspected antiepileptic drug allergy. (?) indicates that the role of SPT and IDT in diagnosis is undetermined. *HLA*, Human leucocyte antigen; *IDT*, intradermal test; *LTA*, lymphocyte toxicity assay; *LTT*, lymphocyte transformation test; *SPT*, skin prick test.

replacement with an alternative drug is needed.¹⁸⁹ However, reactions to multiple AEDs have been reported relatively frequently.^{120,190-198} Clinical cross-reactivity, which frequently occurs from their structural homology, has been reported mainly between the traditional aromatic AEDs, including CBZ, PB, and PHT, but also with newer aromatic AEDs (OXC and LTG) between 15% and 70%, in different studies.^{96,120,163,165,179,198} However, there is large variation in the rate of cross-reactivity among these drugs.¹⁹⁸ In addition, cross-reactivity has also been suggested by positive responses to patch tests and/or the lymphocyte transformation test to more than 1 aromatic AEDs.^{31,63,164,165,179,199-210} More rarely, it was shown that sodium valproate may show patch test cross-reactivity with aromatic AEDs, but clinical cross-reactivity is not determined.¹⁶³ Cross-reactivity between nonaromatic AEDs has not been reported.¹⁷⁹ Of note, these data are often based on single cases, and rarely in the pediatric population. In addition, it has been discussed that the hypersensitivity reaction after administration of a second AED may be a “flare-up” reaction and the second AED will be tolerated again after a longer time has elapsed since the reaction.²¹¹ Cross-reactivity in AED-induced SCARs such as SJS and DRESS has been rarely reported.^{163,174,212} From a practical point of view, avoidance of all aromatic AEDs is usually recommended in patients reacting to one of these drugs.^{110,163,179,213-215} In those patients, VPA, GBP, CLB, LEV, and VGB can be discussed.^{179,197,198}

In selected cases, desensitization can be considered, after re-evaluation of the indication of the treatment and particularly if other AEDs are not efficient. Experience in children remains limited. General protocols for immediate and delayed reactions have been proposed by the European Academy of Allergy and Clinical Immunology.^{216,217} Although desensitization for immediate reactions is an established procedure, the experience regarding desensitization for delayed reactions remains limited, mainly based on case reports and particularly in the pediatric

population.²¹⁷⁻²²¹ Desensitization may be applied in mild delayed reactions such as MPE, nonspecific rash or fixed drug eruption, and selected cases of AGEF. However, severe hypersensitivity reactions such as SJS, TEN, DRESS, vasculitis, and organ-specific reactions are contraindications for desensitization procedure.²¹⁷ Different protocols were applied in case reports and series of patients with HSRs to AEDs, with success rates up to 95%²¹⁷⁻²²¹ (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

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ONLINE REPOSITORY

TABLE E1. An example of a desensitization protocol with oxcarbazepine*

Days	Type of solution	Daily dose increment	Dosage (mg/d)
1-12	A [†]	Increment by 1 mL on each day	0.1-3.2
13-20	B [‡]	Increment by 4 mL on each day	4-32
21-32	C [§]	Increment by 2 mL on each day (to ≤10 mL)	60-120
33-42	O [¶] (2 mL/d) + C	Increment solution C by 2 mL on each day	132
43-52	O (4 mL/d) + C	Increment solution C by 2 mL on each day	252
53-62	O (6 mL/d) + C	Increment solution C by 2 mL on each day	372
63-72	O (8 mL/d) + C	Increment solution C by 2 mL on each day	492
73-82	O (10 mL/d) + C	Increment solution C by 2 mL on each day	612

The dose was increased on each day by adding an increment of 2 mL of solution C, from 2 to 20 mL on a 10-d cycle, which implied an oxcarbazepine daily dose increment of 12 mg.

*Reproduced from Lee J, Park EG, Lee M, Lee J. Desensitization to oxcarbazepine: long-term efficacy and tolerability. J Clin Neurol 2017;13:47-54.

[†]Solution A: 1 mL = 0.1 mg.

[‡]Solution B: 1 mL = 1 mg.

[§]Solution C: 1 mL = 6 mg.

[¶]Solution O: original solution, 1 mL = 60 mg.