Genetic and immune predictors for hypersensitivity syndrome to antiepileptic drugs

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Hypersensitivity syndrome reactions (HSR) to antiepileptic drugs (AED) are associated with severe clinical cutaneous adverse reactions (SCAR). We aimed (1) to assess HSRs to AEDs using the *in vitro* lymphocyte toxicity assay (LTA) in patients who manifested HSRs clinically; (2) to correlate LTA results with the clinical syndrome; (3) to correlate LTA results with the human leukocyte antigen (HLA) allele B*1502 (HLA-B*1502) positivity in a Han Chinese-Canadian population; and (4) to determine the cytokine network in this population. Patients that developed fever and cutaneous eruptions in the presence or absence of organ involvement within 8 weeks of exposure to carbamazepine (CBZ), phenytoin (PHY), or lamotrigine (LTG) were enrolled. Control patients received AEDs without presenting HSR. We investigated 10 CBZ-HSR patients (4 with Stevens-Johnson syndrome (SJS)), 24 CBZ-controls, 10 PHY-HSR patients (4 with drug-induced liver injury (DILI)), 24 PHY-controls,6 LTG-HSR patients (1 with SJS and 1 with DILI), and 24 LTG-controls. There were 30 Han Chinese individuals (14 HSR patients and 16 controls) in our cohort. LTA toxicity greater than 12.5% ± 2.5% was considered positive. Differences among groups were determined by analysis of variance. In addition, we measured cytokine secretion in the patient sera between 1 month and 3 years after the event. All Han Chinese individuals and 30% of Caucasians were genotyped for HLA-B*1502. A perfect correlation ($r = 0.92$) was observed between positive LTA and clinical diagnosis of DILI and SJS/toxic epidermal necrolysis (TEN). HLA-B*1502 positivity in Han Chinese is a predictor of CBZ-HSR and PHY-HSR. HLA-B*1502-negative Han Chinese receiving only CBZ or a combination of CBZ and PHY tolerated the drug(s) clinically, presenting negative CBZ-LTA and PHY-LTA. However, 3 patients presenting negative CBZ-LTA and PHY-LTA, as well as negative HLA-B*1502, showed positive LTG-LTA (38%, 28%, and 25%, respectively), implying that they should not be prescribed LTG. Three patients had LTA positive to both PHY and CBZ, and 3 others had LTA positive to both PHY and LTG. Clinically, all 6 patients presented HSR to both drugs that they tested positive to (cross-reactivity). Patients were grouped based on the clinical presentation of their symptoms as only rash and fever or as a triad of rash, fever and DILI or SJS/TEN that characterizes "true" HSR. Levels of proinflammatory cytokines were significantly higher in patient sera compared with control sera. More specifically, the highest levels of tumor necrosis factor-α have been measured in patients presenting "true" HSR, as were the apoptotic markers Fas, caspase 8 activity, and M30. The LTA is sensitive for DILI and SJS/TEN regardless of drug or patient ethnicity. HSR prediction will prevent AED-

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induced morbidity. In Han Chinese, HLA-B*1502 positivity is a predictor for CBZ-HSR and PHY-HSR. Its negativity does not predict a negative LTG-HSR. There is cross-reactivity between AEDs. Additionally, T-cell cytokines and chemokines control the pathogenesis of SJS/TEN and DILI, contributing to apoptotic processes in the liver and in the skin. (Translational Research 2012;159:397–406)

Abbreviations: ADR = adverse drug reaction; AED = antiepileptic drug; CBZ = carbamazepine; DIHS = drug-induced hypersensitivity syndrome; DILI = drug-induced liver injury; DRESS = drug rash with eosinophilia and systemic symptoms; Fas = CD95, APO-I; HLA = human leukocyte antigen; HSR = hypersensitivity syndrome reaction; IL = interleukin; LTA = lymphocyte toxicity assay; LTG = lamotrigine; M30 = mitochondrial marker for apoptosis (cytokeratine 18); MHC = major histocompatibility complex; ox-CBZ = oxcarbazepine; PHY = phenytoin; RANTES = regulated upon activation normal T-cell expressed and secreted; SCAR = severe cutaneous adverse reactions; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; Th = T helper response; TNF-α = tumor necrosis factor- α

AT A GLANCE COMMENTARY

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Serious adverse drug reactions are a major cause of morbidity and mortality worldwide. The identification of predisposing genotypes may improve patient management. Immune-mediated drug hypersensitivity reactions are uncommon adverse events restricted to a subset of vulnerable patients and pharmaceutical products including antiepileptics. Nevertheless, such reactions are potentially life threatening and have a tremendous impact on clinical practice. In 1998 alone, immune-mediated reactions accounted for 13,000 to 230,000 hospital admissions in the United States, with estimated attendant costs of $275 to $600 million annually. Moreover, it reduced the bound of trust between the patient and his physician. This works brings a translational research and laboratory diagnostic approach to the clinical diagnosis.

Increasing knowledge about the mechanisms involved in the development of seizures, as well as improved understanding of the cellular effects of antiepileptic drugs (AED), have resulted in links between demonstrated molecular actions of these drugs and the types of seizures against which they are effective. A number of AEDs have been synthesized, with the goal of adapting synaptic function to regulate seizure frequency or occurrence. "First generation" AEDs include carbamazepine (CBZ), phenytoin (PHY), phenobarbital, and valporate, whereas felbamate, gabapentin, lamotrigine (LTG), topiramate, levitracetam, oxcarbazepine (ox-CBZ), and zonisamide are classified as "second generation" AEDs. Aromatic AEDs include CBZ, PHY, and phenobarbital.[1] CBZ and PHY are structurally related to one another, while LTG is not. PHY is para-hydroxylated by cytochrome p450s primarily to 2 enantiomers, and further metabolized to a catechol that spontaneously oxidizes to semiquinone and quinine species.[2-4] Major CBZ metabolism pathways include oxidation, hydration to 2- and 3-hydroxy-CBZ, which can be further oxidized to a catechol or an iminoquinone.[5,6] LTG is largely metabolized in the liver by glucuronic acid conjugation, producing a 2-N-glucuronide conjugate, which can be hydrolyzed to beta-glucuronidase.[7]

Interactions between AEDs are important in examining drug function and metabolism. CBZ and PHY decrease the half-life of LTG in the body, while valporate increases it.[8]

Hypersensitivity reactions (HSR) are a common feature of anticonvulsants, being noted in 30% and 70% of patients with drug-induced liver injury (DILI) caused by CBZ and PHY, respectively.[9,10] To establish whether a drug is the cause of an immune-mediated reaction, alternative causes, latency of a reaction after drug intake, improvement after drug cessation, previous patient cases, and rechallenge have to be examined.[9]

CBZ, PHY, and LTG have been associated with HSRs. LTG was reported to produce Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and DILI.[11-13] Most HSR cases occur during the first 8 weeks of treatment.[14-17] HSRs refer to dose-independent, idiosyncratic, severe adverse drug reactions (ADR).[18,19] Clinically, a triad of fever, rash, and organ involvement defines a "true" HSR.[9,18,20,21]

Skin manifestations include exanthematous rash, blistering eruptions such as erythema multiforme, SJS, and TEN.[16,22-25] SJS and TEN are severe cutaneous adverse reactions (SCAR).[26-34] Epidermal detachment below