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ANTICONVULSANT DRUGS

GENETIC FACTORS ASSOCIATED WITH PHENYTOIN-RELATED SKIN REACTIONS

Investigators at the Taipei Medical University Hospital and other centers in Taiwan conducted a case-control study in 2002-2014 among 105 cases with phenytoin-related severe cutaneous adverse reactions (n=61 Stevens-Johnson syndrome/toxic epidermal necrolysis and n=44 drug reactions with eosinophilia and systemic symptoms), 78 cases with maculopapular exanthema, 130 phenytoin-tolerant control participants, and 3655 population controls from Taiwan, Japan, and Malaysia. A genome-wide association study (GWAS), direct sequencing of the associated loci, and replication analysis discovered a cluster of 16 single-nucleotide polymorphisms in CYP2C genes at 10q23.33 that reached genome-wide significance. Direct sequencing of CYP2C identified a missense variant that showed significant association with phenytoin-related severe cutaneous adverse reactions. A meta-analysis using the data from all three populations showed an overall odds ratio of 11 (P< .00001) for CYP2C9*3 association with phenytoin-related severe cutaneous adverse reactions. Delayed clearance of plasma phenytoin was detected in patients with severe skin reactions, especially CYP2C9*3 carriers. (Chung W-H, Chang W-C, Lee Y-S, et al; for the Taiwan Severe Cutaneous Adverse Reaction Consortium and the Japan Pharmacogenomics Data Science Consortium. **JAMA** 2014 Aug 6;312(5):525-34).

COMMENTARY. Phenytoin-associated hypersensitivity skin reactions are a serious and sometimes fatal adverse side effect. Anticonvulsants with a lesser or no tendency to hypersensitivity skin reactions include levetiracetam, topamax, vigabatrin,

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ethosuximide, and gabapentin. Anticonvulsants in addition to phenytoin with increased risk of erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) include carbamazepine, oxcarbazepine, valproate, phenobarbital, and lamotrigine. The combination of carbamazepine and acetaminophen further increases the risk of hypersensitivity skin reactions [1]. Erythema multiforme as a synergistic side effect to a combination of phenytoin therapy and cranial radiotherapy is also reported [2]. The routine use of postoperative phenytoin as a prophylactic anticonvulsant in the absence of a history of seizures is discouraged [3][4].

The US FDA cautions that phenytoin or fosphenytoin should not be prescribed as an alternative to carbamazepine in patients who carry HLA-B*15.02, although the association with severe cutaneous reactions in Asians is weaker than that found with carbamazepine [5]. Current studies find that the HLA-DRB1*15.01 allele is a risk factor for AED-induced SJS/TEN among Han Chinese, whereas HLA-A*33.03, HLA-B*58.01, and HLA-DRB1*03.01 alleles may be protectors against AED-induced skin reactions, especially CBZ-SJS/TEN [6]. Patients of Han ethnicity living in northeastern China and having EPHX1 c.337T>C polymorphisms also show an increased risk of developing CBZ-SJS/TEN, related to an increased concentration of a CBZ metabolite, CBZ-10,11-epoxide [7]. The discovery of a functional link of genetic variants to the phenytoin, carbamazepine, and other aromatic AED-related hypersensitivity cutaneous reactions might lead to prospective preventive genetic testing.

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VALPROATE-INDUCED REVERSIBLE BRAIN ATROPHY AND COGNITIVE DETERIORATION

Pediatric neurologists at Dalhousie University, Halifax, Nova Scotia, report an 8-year-old boy with rapid cognitive decline after a year-long course of valproate in varying dosages for myoclonic and atypical absence seizures. Sequential MRIs over a 1-year seizure free period revealed progressive brain atrophy and white matter signal changes. MR spectroscopy while taking valproate showed a normal lactate peak and a decreased N-acetylaspartate to creatine ratio. Tests for mitochondrial or neurodegenerative diseases and liver transaminases were normal. POLG gene testing detected no pathogenic variant. After discontinuing valproate, MRI and MR Spectroscopy, and cognitive and school function returned to baseline. He is currently seizure-free while taking clobazam monotherapy. (Lovett M, Skidmore DL, Mohamed IS. Valproate-induced pseudoatrophy: Expanding the clinical and imaging spectrum. **Pediatr Neurol** 2014 Aug;51(2):284-5).

COMMENTARY. Four types of valproate-induced encephalopathy are described: 1) Direct toxic encephalopathy; 2) hyperammonemic encephalopathy; 3) hepatic