Study identifies genetic variants linked with severe skin reactions to antiepileptic drug

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Researchers have identified genetic variants that are associated with severe adverse skin reactions to the antiepileptic drug phenytoin, according to a study in the August 6 issue of *JAMA*.

Phenytoin is a widely prescribed antiepileptic drug and remains the most frequently used first-line antiepileptic drug in hospitalized patients. Although effective for treating neurological diseases, phenytoin can cause cutaneous (skin) adverse reactions ranging from mild to severe. The pharmacogenomic basis of phenytoin-related severe cutaneous adverse reactions has not been known, according to background information in the article.

Wen-Hung Chung, M.D., Ph.D., of Chang Gung Memorial Hospital, Keelung, Taiwan, and colleagues investigated the genetic factors associated with phenytoin-related severe cutaneous adverse reactions. The case-control study was conducted 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 (a less severe type of rash), 130 phenytoin-tolerant control participants, and 3,655 population controls from Taiwan, Japan, and Malaysia. A genome-wide association study (GWAS) was conducted using the samples from Taiwan. The initial GWAS included samples of 60 cases with phenytoin-related severe cutaneous adverse reactions and 412 population controls from Taiwan.

Analysis of the data indicated that variants of the gene CYP2C, including CYP2C9*3, were associated with phenytoin-related severe cutaneous adverse reactions. The statistically significant association between CYP2C9*3, known to reduce drug clearance (the elimination of a drug from the body), and phenytoin-related severe cutaneous adverse reactions was replicated by the samples from Taiwan, Japan, and Malaysia, with a meta-analysis showing an 11 times higher odds of experiencing this reaction with this variant. Delayed clearance of plasma phenytoin was detected in patients with severe cutaneous adverse reactions, especially CYP2C9*3 carriers, providing a clinical link of the associated variants to the disease.

Delayed clearance was also noted in patients with severe cutaneous adverse reactions without CYP2C9*3, suggesting that nongenetic factors such as renal insufficiency, hepatic dysfunction, and concurrent use of substances that compete or inhibit the enzymes may also affect phenytoin metabolism and contribute to severe cutaneous adverse reactions.

"This study identified CYP2C variants, including CYP2C9*3, known to reduce drug clearance, as important genetic factors associated with phenytoin-related severe cutaneous adverse reactions. These findings may have potential to improve the safety profile of phenytoin in clinical practice and offer the possibility of prospective testing for preventing phenytoin-related severe cutaneous adverse reactions. More research is required to replicate the genetic association in different populations and to determine the test characteristics and clinical utility," the authors conclude.

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