

DRUG RESISTANT EPILEPSY: A COMPLIANCE PROBLEM OR AN ABNORMALITY OF TRANSPORT PROTEINS?

Association of Multidrug Resistance in Epilepsy with a Polymorphism in the Drug-transporter Gene *ABCB1*

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N Engl J Med 2003;348(15):1442–1448

PURPOSE: One third of patients with epilepsy have drug-resistant epilepsy, which is associated with an increased risk of death and debilitating psychosocial consequences. Because this form is resistant to multiple antiepileptic drugs (AEDs), the mode of resistance must be nonspecific, involving drug-efflux transporters such as adenosine triphosphate (ATP)-binding cassette subfamily B member 1 (*ABCB1*, also known as MDR1 and P-glycoprotein 170). We hypothesized that the CC genotype at the *ABCB1* C3435T polymorphism, which is associated with increased expression of the protein, influences the response to AED treatment.

METHODS: *ABCB1* 3435 was genotyped in 315 patients with epilepsy, classified as drug-resistant in 200 and drug-responsive in 115, and 200 control subjects without epilepsy. Recently devised methods were used to control for population stratification, and linkage disequilibrium was calculated across the gene.

RESULTS: As compared with patients with drug-responsive epilepsy, patients with drug-resistant epilepsy were more likely to have the CC genotype at *ABCB1* 3435 than the TT genotype (odds ratio, 2.66; 95% confidence interval, 1.32–5.38; $P = 0.006$). No genetic stratification was found between the two groups of patients. The polymorphism fell within an extensive block of linkage disequilibrium spanning much or all of the gene, implying that the polymorphism may not itself be causal but rather may be linked with the causal variant.

CONCLUSIONS: These pharmacogenomic results identify a genetic factor associated with resistance to AEDs.

COMMENTARY

One of the most curious and frustrating aspects of epilepsy is the subset of patients who are refractory and do not respond to any anticonvulsant drug. Physicians have been fortunate to have many new agents for epilepsy introduced in the past decade. These drugs have shown real advances in convenience as well as in reducing adverse effects and long-term toxicity, compared with previously available agents. Unfortunately, although a few previously refractory patients become seizure free with these new drugs, this outcome is rare. Much is written about differing mechanisms and rational polypharmacy. However, patients for whom any drug fails because of lack of efficacy (and not because of adverse effects) are unlikely to respond completely to any other drug (1). The research by Siddiqui and colleagues gives us an intriguing, and potentially critical, insight into the reason for this puzzling failure of multiple, diverse medications.

Siddiqui et al. compared patients with refractory epilepsy with those whose epilepsy is pharmacologically well controlled. They found that significant differences occurred between groups in the genotype of a drug-efflux transporter protein. A similar difference was found when drug-resistant patients were compared with normal control subjects.

This study is intriguing because it suggests a common mechanism for drug resistance in patients with diverse seizure disorders. In other words, it may not be the epilepsy itself that is more severe but a difference in patient genotype. It is not clear from the article whether subpopulations of seizure types are more at risk for drug resistance—although all seizure types were included, subpopulations were not analyzed. Similarly, whereas the results suggest that the specific drug used is not important, a subanalysis of drugs was not performed. It may be that certain drugs are less dependent on transporter proteins. The authors discuss that this conjecture, theoretically, could be true. If so, drugs that are less dependent on transporter proteins may be more likely to be effective in patients who are refractory or who are known to have deficiencies in transporter proteins. These are important questions to be addressed in future studies.

The particular alleles studied by Siddiqui et al. are by no means the answer to the drug-resistance question. Although statistical differences were found between drug-refractory and

drug-responsive patients, the subtype seen more commonly in drug-resistant patients was found in only 27% of these patients and occurred in 16% of drug-responsive and 18% of normal subjects. The results, therefore, are far from a diagnostic test for drug resistance. However, this first step in the definition of drug-transporter gene polymorphisms we hope will lead to further investigations in this area. New research might well result in practical clinical applications of this finding, including screening for at-risk patients and, more important, strategies to

combat known drug resistance. Such a novel approach is clearly needed in finding new treatments for the many patients who continue to have refractory epilepsy.

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Reference

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.