Indian J Med Res 134, September 2011, pp 253-255

Commentary

Genetic polymorphism of drug refractory epilepsy

Epilepsy is a common neurological disorder affecting over 50 million people worldwide with distinct symptoms, aetiology and prognosis. In India, it is estimated that there are 55,00,000 persons with epilepsy and prevalence rate of epilepsy is 5.59 per 1,000 population[1]. Current treatment regimens for epilepsy focus on seizure suppression or prorogation. Although epileptic seizures can be effectively controlled with anti-epileptic drugs (AEDs) in up to 70-80 per cent of patients, about one third of patients are drug-refractory despite optimal AED treatment[2].

An important characteristic of drug resistant epilepsy is that many patients are resistant to several, if not all anti-epileptic drugs (AEDs). Based on several studies it was reported that patients who fail to respond to first-line or second-line AED therapy will develop drug resistance, even on using AEDs acting via diverse mechanisms[3]. Drug-resistant epilepsy affects individual health and the quality of life, with heavy burden on society. Studies have shown that drug refractory epilepsy imposes serious threats to patient's life which include neuropsychological illness, psychiatric and social impairment, reduced marriage rates and decreased life span[4]. Further, only a subgroup of refractory patients responds to surgery or other specialized treatments and make them seizure free but others will continue to have seizures[2]. Identifying the factors that contribute to drug resistance is, therefore, a major challenge, with a potentially significant impact on clinical practice.

The plausible factors for drug resistance could be environmental and seizure related causes. But, there are reports conferring running of epilepsy among families, indicating a possible genetic cause for the disease. Genetic causes have gained attention for both epilepsy as well as drug resistance. For various cases, the causes and response to treatment are closely related. This holds true for various sodium channel mutations implicated in disease and also acting as novel targets for various AEDs. Identification of predictive markers for drug resistance may revolutionize the existing treatment strategies. There are reports about the associations between many genetic variations and clinical drug resistance; however, none of these associations has been unequivocally replicated[5]. Two separate studies done in south and north Indian patients were also not able to find any evidence for association[6,7]. Therefore, further exhaustive studies about the influence of genetic variations on drug resistance may be valuable.

The two well known hypotheses for understanding the biological mechanism underlying multidrug resistance are the target and transporter hypotheses[3,8]. In target hypothesis, epilepsy-induced alterations in specific drug targets (reduction in sensitivity) such as sodium channels have also been a major cause for pharmacoresistant epilepsy[9]. Transporter hypothesis suggests that increased expression of efflux transporter p-glycoprotein (P-gp), encoded by ATP binding cassette *(ABCB1)* gene, leads to decreased bioavailability and limited brain access of antiepileptic drugs that may result in drug resistance. As we know, AEDs are lipophilic in nature and P-gp transporters have a wide variety of specificity for lipohilic molecules[10] but still, most commonly used anticonvulsants namely carbamazepine and sodium valproate were not found to be a substrate to P-gp[11,12]. Phenytoin was shown to be a weak substrate of P-gp and non-ABC transporter such as RLIP76 may also be involved in transporting this drug in blood brain barrier[13]. Thus, there may be alternative mechanisms behind the development of drug resistance to these specific drugs which needs to be explored[11].

Recently, CYP2C19 a polymorphic drug metabolizing enzyme (DME) was shown to be

associated with clobazam response[14]. The responder rate was significantly greater in *CYP2C19* poor metabolizers and *CYP2C19* heterozygous extensive metabolizer than in *CYP2C19* homozygous extensive metabolizers. However, studies are sparse which demonstrate the association between multiple AEDs resistance and drug metabolizing enzymes. A study by Ufer *et al*[15] showed that heterozygous *CYP2C9*3* were under-represented among non-responders to AEDs in Caucasians epileptic patients.

In this issue, Lakhan *et al*[16] explored the possible association between *CYP2C* gene polymorphisms and resistances to AEDs in Indian epileptic patients. Authors have shown the distribution of variant genotypes of *CYP2C9* and *CYP2C19* in patients with drug resistance and responder to AEDs. They observed *CYP2C9*3* variant allele frequency was under-represented in drug resistant patients compared to responder patients. They did not find any significant association between variants of *CYP2C19* in drug resistance/responder. Hence, it was suggested that the carrier of *CYP2C9*3* may contribute towards lower risk for developing multiple drug resistance in epileptic patients. In Indian population, the frequency of *CYP2C9*3* was 8 per cent[17]. A recent study by Kesavan *et al*[18] demonstrated the association of *CYP2C9*3* in development of phenytoin-induced neurological toxicity in Indian population. However, the clinical significance of these studies should be carefully interpreted. Multicentric studies in large number of samples involving all major ethnic groups in India are needed to confirm these findings. If we find positive association with high degree of statistical significance, screening for *CYP2C9*3* genotype may help the clinicians in predicting the responders and non-responders for AEDs as well as risk for developing phenytoin toxicity.

The database for variant alleles of genes encoding for drug metabolizing enzymes, transporters and channels (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, EPHX1, UGT1A1, UGT2B7, MDR1, SCN1A, SCN1B, and SCN2A) are available for healthy volunteers[17,19,20] as well as for Indian epileptic patients[21]. This information may be useful for future studies of drug resistance in epilepsy. Not only the candidate gene studies but also whole exome sequencing (WES), transcriptional studies in surgery-resected brain tissue from patients with drug-resistant epilepsies, gene expression studies and multidisciplinary approaches, including neuropathology and imaging are important to understand their mechanisms.

R. Kesavan[*], Ritushree Kukreti[**] & C. Adithan[*,+]

[*]Center for Advanced Research
in Pharmacogenomics
Department of Pharmacology
Jawaharlal Institute of Postgraduate
Medical Education & Research
Puducherry 605 006

[**]Genomics & Molecular Medicine,
Institute of Genomics & Integrative Biology
Mall Road, Delhi 110 007, India

[+]*For correspondence*:
adithan@yahoo.com

References

1. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. *Epilepsia* 1999; *40* : 631-6.
2. Depondt C, Shorvon SD. Genetic association studies in epilepsy pharmacogenomics: lessons learnt and potential applications. *Pharmacogenomics* 2006; *7* : 731-45.
3. Kasperaviciute D, Sisodiya SM. Epilepsy pharmacogenetics. *Pharmacogenomics* 2009; *10* : 817-36.
4. Sperling MR. The consequences of uncontrolled epilepsy. *CNS Spectr* 2004; *9* : 98-9.
5. Sisodiya SM. Genetics of drug resistance. *Epilepsia* 2005; *46* : 33-8.
6. Lakhan R, Misra UK, Kalita J, Pradhan S, Gogtay NJ, Singh MK, *et al*. No association of *ABCB1* polymorphisms with drug-refractory epilepsy in a north Indian population. *Epilepsy Behav* 2009; *14* : 78-82.
7. Vahab SA, Sen S, Ravindran N, Mony S, Mathew A, Vijayan N, *et al*. Analysis of genotype and haplotype effects of *ABCB1* (MDR1) polymorphisms in the risk of medically refractory epilepsy in an Indian population. *Drug Metab Pharmacokinet* 2009; *24* : 255-60.
8. Rogawski MA, Johnson MR. Intrinsic severity as a determinant of antiepileptic drug refractoriness. *Epilepsy Curr* 2008; *8* : 127-30.
9. Kwan P, Poon WS, Ng HK, Kang DE, Wong V, Ng PW, *et al*. Multidrug resistance in epilepsy and polymorphisms in the voltage-gated sodium channel genes *SCN1A, SCN2A,* and *SCN3A*: correlation among phenotype, genotype, and mRNA expression. *Pharmacogenet Genomics* 2008; *18* : 989-98.
10. Schmidt D, Loscher W. Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. *Epilepsia* 2005; *46* : 858-77.
11. Owen A, Pirmohamed M, Tettey JN, Morgan P, Chadwick D, Park BK. Carbamazepine is not a substrate for P-glycoprotein. *Br J Clin Pharmacol* 2001; *51* : 345-9.
12. Margineanu D, Klitgaard H. Mechanisms of drug resistance in epilepsy: relevance for antiepileptic drug discovery. *Expert Opin Drug Discovery* 2009; *4* : 23-32.
13. Awasthi S, Hallene KL, Fazio V, Singhal SS, Cucullo L, Awasthi YC, *et al*. RLIP76, a non-ABC transporter, and drug resistance in epilepsy. *BMC Neurosci* 2005; *6* : 61.

14. Seo T, Nagata R, Ishitsu T, Murata T, Takaishi C, Hori M, *et al*. Impact of *CYP2C19* polymorphisms on the efficacy of clobazam therapy. *Pharmacogenomics* 2008; *9* : 527-37.
15. Ufer M, Mosyagin I, Muhle H, Jacobsen T, Haenisch S, Hasler R, *et al* .Non-response to antiepileptic pharmacotherapy is associated with the ABCC2 -24C>T polymorphism in young and adult patients with epilepsy. *Pharmacogenet Genomics* 2009; *19* : 353-62.
16. Lakhan R, Kumari K, Singh K, Kalita J, Misra UK, Mittal B. Possible role of *CYP2C9* & *CYP2C19* single nucleotide polymorphisms in drug refractory epilepsy. *Indian J Med Res* 2011; *134* : 295-301.
17. Jose R, Chandrasekaran A, Sam SS, Gerard N, Chanolean S, Abraham BK, *et al*. *CYP2C9* and *CYP2C19* genetic polymorphisms: frequencies in the south Indian population. *Fundam Clin Pharmacol* 2005; *19* : 101-5.
18. Kesavan R, Narayan SK, Adithan C. Influence of *CYP2C9* and *CYP2C19* genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients. *Eur J Clin Pharmacol* 2010; *66* : 689-96.
19. Ramasamy K, Sisy SS, Chandrasekaran A. Allele and genotype frequency of MDR1 C3435T in Tamilian population. *Drug Metab Pharmacokinet* 2006; *21* : 506-8.
20. Krishnakumar D, Gurusamy U, Dhandapani K, Surendiran A, Baghel R, Kukreti R, *et al*. Genetic polymorphisms of drug-metabolizing phase I enzymes CYP2E1, CYP2A6 and CYP3A5 in South Indian population. *Fundam Clin Pharmacol* 2011; doi: 10.1111/j.1472-8206.2010.00917.x.
21. Grover S, Gourie-Devi M, Baghel R, Sharma S, Bala K, Gupta M, *et al*. Genetic profile of patients with epilepsy on first-line antiepileptic drugs and potential directions for personalized treatment. *Pharmacogenomics* 2010; *11* : 927-41.