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Lack of Association between Polymorphism in ABCC2 Gene and Response to Antiepileptic Drug Treatment in Croatian Patients with Epilepsy

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A B S T R A C T

Despite advances in antiepileptic drug (AED) therapy, about one-third of patients with epilepsy are resistant to drug treatment. Functional impact of polymorphisms in drug-efflux transporter genes may contribute to multidrug resistance theory. Studies on ABCB1 gene gave contradictory results and available data suggest that this polymorphism may not directly cause altered P-glycoprotein (Pgp) transport activity but may be associated with one or more causal variants in the stretch of linkage disequilibrium or is caused by multiple gene polymorphisms. Genetic polymorphisms also occur frequently in other transmembrane transport systems including the multidrug resistance proteins (MRPs, ABCC2). The aim of this research was to investigate the possible association of ABCC2 gene polymorphisms G1249A in exon 10 and C24T in exon 1 with the development of drug resistance. This cross-sectional study is a part of ongoing pharmacogenomic study of epilepsy in Croatian population. All patients enrolled in the study had an established diagnosis of partial complex epilepsy with or without secondary generalization with non lesional brain MRI with epilepsy protocol and have been suffering for more than two years. They were divided into two groups. The first group comprised 52 patients refractory to the current therapy, while the second group consisted of 45 patients with well-controlled seizures. Our data did not identify any significant association between genetic polymorphisms of exon 1 (24C>T) and exon 10 (1249G<A) of ABCC2 gene or any combined effect in response to AED treatment and development of drug resistance in patients with partial complex epilepsy. Statistical significant difference was not found in genotype based analysis, allele frequency, haplotype and combined genotype analysis.

***Key words**: ABCC2 gene, genetic polymorphism, multi-drug resistance, epilepsy, cryptogenic*

Introduction

Epilepsy is one of the most common neurological disorders[1]. Despite advances in antiepileptic drug (AED) therapy about one-third of patients with epilepsy are resistant to drug treatment[2]. The consequences of uncontrolled epilepsy can be severe and include shortened lifespan, bodily injury, neuropsychological and psychiatric impairment and social disability[3]. Most patients with refractory epilepsy are resistant to several, if not all AEDs, despite the fact that these drugs act by different mechanisms[2,4]. This multidrug type of resistance could argue against epilepsy-induced alterations in specific drug targets as the main cause of pharmacoresistant epilepsy pointing instead to nonspecific and possibly adaptive mechanisms[4]. It was found that gene polymorphism was found that may influence the severity of disease in some non-epileptic disorders[5–7]. Epilepsy was the first disorder of central nervous system in which the drug resistance was associated with enhanced expression of multidrug transporters in the brain[8]. Multidrug transporters, such as P-glycoprotein, multidrug resistance protein 1 (MRP1) and multidrug resistance protein 2 (MRP2) and their genes are overexpressed in capillary endothelial cells and

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astrocytes in epileptogenic brain tissue from patients with medically intractable epilepsy[9-13]. The expression of multidrug transporters in the astroglial end-feet covering the blood vessels that is found in epileptogenic brain tissue might represent a 'second barrier' under these conditions[11,14]. Several widely used AEDs, which have been made lipophilic to allow them to penetrate the brain, are substrates for Pgp and/or MRPs in the blood-brain barrier[8,15-21]. Therefore, the overexpression of these transporters in epileptogenic tissue is likely to reduce the amount of drug that reaches the epileptic neurons. This is one plausible explanation for multidrug resistance in epilepsy[4]. Functional impact of polymorphisms in drug--efflux transporter genes can also contribute to multidrug resistance theory. Studies on ABCB1 gene gave contradictory results and available data suggest that this polymorphism may not directly cause altered Pgp transport activity but may be associated with one or more causal variants in the stretch of linkage disequilibrium (LD) or is caused by multiple gene polymorphisms. Genetic polymorphisms also occur frequently in other transmembrane transport systems including the MRPs[22-24]. ABCC2 polymorphism 24C/T is associated with variable pharmacokinetic parameters of mycophenolic acid, methotrexate, irinotecan, diclofenac and toxic liver injury[25-28] and for 1249 G/A ABCC2 polymorphism was found to be associated with pharmacokinetics of tenofovir, talinolol and toxic liver injury[25,29,30]. The aim of this research was to investigate the possible association of ABCC2 gene polymorphisms G1249A in exon 10 and C24T in exon 1 with the development of drug resistance.

Patients and Methods

Patients

This cross-sectional study is a part of ongoing pharmacogenomic study of epilepsy in Croatian population and has been approved by the Ethics Committee of Zagreb University Hospital Center. Patients were consecutively recruited through the Referral Epilepsy Center Department of Neurology and genotyping was performed in Department for Functional Genomics, Clinical Institute of Laboratory Diagnosis. All patients enrolled in the study had an established diagnosis of partial complex epilepsy with or without secondary generalization and have been suffering for more than two years. Non-lesional brain MRI with epilepsy protocol was including criteria and patients were in age between 16–66 years. They were divided into two groups. The first group consisted of 52 patients refractory to the current therapy, while the second group consisted of 45 patients with well-controlled seizures. Refractory epilepsy was defined as one or more seizures per month during last one year, with two or more established AED at the maximally tolerated doses in therapy. Patients with well-controlled seizures were without seizures in same period. Compliance was determined by measuring concentration of anticonvulsants in the serum. Seizure frequency was recorded from the patient's medical records, seizure diaries and patient interview. Patients who were between these two groups were excluded from the study. Patients with history of central nervous system infection, head trauma, brain tumor, cerebrovascular disease, neurodegenerative and psychiatric diseases, pseudo-attacks were excluded from the study. All patients have signed informed consent to participate in this study.

Non-responders took significantly higher number of antiepileptics (χ^2=55.322, ss=4, p<0.001) 2.9, while responders took 1.9 antiepileptics. The mean age was 42.64 years (SD 13.91). Most of patients were taking one antiepileptic drug that is substrate of MRP2 (65% of non-responders, and 72% of responders). 30% of non-responders and 14% of responders were taking two antiepileptic drugs that are substrates of MRP2. We did not find significant difference in the mean number of antiepileptic drugs in both groups (χ^2=5.345, ss=2, p>0.05). Carbamazepine was the most frequently administrated antiepileptic (95 patients – 88%), either as monotherapy or in combination with other drugs. 54 (50.5%) patients were using lamotrigine, 46 (43%) phenobarbital, 23 (21%) valproate and 18 (16.8%) of patients were treated with topiramate. Gabapentin and phenytoin were antiepileptic drugs in 7 and 6 patients.

Methods

Genotyping of ABCC2-24C>T and 1249G>A was performed by methods based on polymerase chain reaction followed by restriction fragment length polymorphism (PCR-RFLP), previously described by Mor-Cohen et al.[31] and Naesen et al.[28]

Statistical analysis

A test for Hardy-Weinberg equilibrium using Markov chain method[32], as well as linkage-disequilibrium likelihood-ratio test between loci whose gametic phase is unknown[33] were performed, as implemented in Arlequin ver. 3.01[34]. Haplotype frequencies were estimated using Expectation-Maximization algorithm implemented in the same program, leading to maximum likelihood estimates of haplotype frequency. χ^2-test was used for pair-wise comparisons of the allele frequencies among groups. Log likelihood ratio tests were performed to compare distributions of the estimated haplotypes among groups, as well as comparisons of genotype frequencies. P values of less than 0.05 were considered statistically significant. χ^2- or t-tests were performed for comparisons of duration of epilepsy, antiepileptic drugs and MRP2 substrates between genotypes and between resistant vs. non resistant patients. All statistical analyses were carried out using SPSS 11.5 (SSPS inc., Chicago, IL, USA) statistical software package. Pattern was calculated with Altman's algorithm and power of 80%.

Results

Genotype frequencies of the ABCC2 24CC, 24CT and 24TT in the sample were 47, 41 and 6 respectively and of the ABCC2 1249GG, 1249AG and 1249AA genotypes were 52, 35 and 10, respectively.

TABLE 1
DISTRIBUTION OF ALLELE AND GENOTYPE FREQUENCIES OF ABCC2 24C>T AND 1249G>A BETWEEN SUBJECTS WHO ARE RESISTANT AND NON RESISTANT TO TREATMENT

Locus			Resistant N=52	Non resistant N=45	OR (95%C.I.)
exon 1 C24T	[a]Allele	C	72	63	1.01 (0.84–1.20)
		T	28	25	1
	[b]Genotype	CC	26	21	1
		CT	20	21	0.77 (0.33–1.78)
		TT	4	2	1.62 (0.27–9.70)
exon 10 G1249A	[a]Allele	A	32	23	1.29 (0.76–1.90)
		G	72	67	1
	[b]Genotype	AA	7	3	1
		GA	18	17	0.45 (0.10–2.05)
		GG	27	25	0.46 (0.11–1.99)

[a] exon 1 -24C>T, p=0.920, χ^2 =0.01, SS=1; exon 10 1249G>A, p=0.52, χ^2=0.415, ss=1
[b] exon 1 -24C>T, p=0.683, Likelihood ratio G=0.854, ss=2; exon 10 1249G>A, p=0.606, Likelihood ratio G=1.246, ss=2

TABLE 2
DISTRIBUTION OF HAPLOTYPE FREQUENCIES OF ABCC2 24C>T AND 1249G>A BETWEEN SUBJECTS WHO ARE RESISTANT AND NON RESISTANT TO TREATMENT

Haplotype	C24T	G1249A	Resistant N=52	Non resistant N=45	OR (95%C.I.)
H1	C	G	49.33	46.44	1
H2	C	A	22.67	16.56	1.29 80.52–3.16)
H3	T	G	21.67	18.56	1.09 (0.49–2.48)
H4	T	A	6.33	6.44	0.93 (0.20–4.22)

Likelihood ratio G=0.3295; ss=3; p=0.954

No significant deviations from the expected Hardy-Weinberg proportions were observed in the total sample (exon 1 C-24T: p=0.125; exon 10 G1249A: p=0.218), and in resistant and non resistant patients. Test result for linkage disequilibrium between loci was not found to be significant (LD – χ^2=1.57, p<0.45, ss=2).

Pair-wise comparisons of the allele frequency between resistant and non resistant patients did not revealed statistical differences for both loci (χ^2 test, exon 1 C-24T, p=0.92; exon 10 G1249A, p=0.52). The same negative results were found in genotype based analysis of exon 1 C-24T and exon 10 G1249A. Likelihood ratio, G test; exon 1 C24T, p=0.683, Likelihood ratio G=0.854, ss=2; exon 10 G1249A, p=0.606, Likelihood ratio G=1.246, ss=2 (Table 1).

Likewise, no statistical differences were observed in distributions of the estimated haplotypes between those groups. Likelihood ratio G=0.3295; ss=3; p=0.954 (Table 2), and in analyses of genotype combination frequencies of ABCC2 24C>T and 1249G>A between subjects who are resistant and non resistant to treatment. Likelihood ratio G=3.447, ss= 3, p=0.651 (Table 3).

There were significant differences between resistant and non resistant patients in the age of the onset of illness ($\overline{X}$ ages ± SD were 11.8 ± SD 6.37 *vs*. 23.4 ± SD 11.57, t=8,448, ss=105, p<0.001) in resistant and non resistant patients, respectively and duration of illness ($\overline{X}$ values ± SD were 30.4 ± SD 11.97 *vs*. 19.9 ± SD 11.59, t=4,495, ss=105, p<0.001) in resistant and non resistant group, respectively.

Discussion

ABCC2 gene encoded MRP2 transmembrane protein may have a potential role in the modulation of brain penetration of antiepileptic drugs[17–21]. We studied C24T and G1249A polymorphisms of ABCC2 gene on exon 1 and 10 because they are the most common polymorphic variants for which association with pharmacokinetics of some cytostatic drugs was documented. Negative brain MRI was including criteria because numerous clinical and pathological factors can contribute to drug resistance in symptomatic epilepsy, especially with pathological findings of hippocampal sclerosis, cortical dysplasia, severe brain injury, because they are more drug resistant than idiopathic or cryptogenic epilepsy[35]. However, negative MRI finding could not exclude the possibility that symptomatic epileptogenic lesion known for causing pharmacoresistance exists despite normal MRI because it can depend on strength of machine.

Our data did not identify any significant association between genetic polymorphisms of exon 1 24C>T and

TABLE 3
DISTRIBUTION OF GENOTYPE COMBINATION FREQUENCIES OF ABCC2 24C>T AND 1249G>A BETWEEN SUBJECTS WHO ARE RESISTANT AND NON RESISTANT TO TREATMENT

Genotype combination	Resistant N=52	Non resistant N=45	OR (95%C.I.) p
CC-GG	13	12	1
CC–GA	10	8	1.15 (0.34–3.89), p=0.818
CT–GG	11	10	1.02 (0.32–3.24), p=0.979
CT–GA	6	9	0.62 (0.17–2.25), p=0.463
other	11	5	2.03 (0.54–7.57), p=0.292

Likelihood ratio G=3.447, ss=3, p=0.651

exon 10 1249G>A of ABCC2 gene or any combined effect in response to AED treatment. Statistical significant difference was not found in genotype based analysis, allele frequency, haplotype and combined genotype analysis. Several explanations are possible for this lack of association. Phenytoin and carbamazepine are suggested as a substrates of both Pgp and MRP2 and valproic acid is suggested as a substrate of MRP2[16–18,21,35–37]. Some experimental studies have doubted the fundamental facts that most AEDs are substrates of ABC transporters[38]. Although a number of AEDs have been identified as substrates of ABC transporters in rodent models, recent experimental models have demonstrated significant differences in the efflux transport of AEDs by ABC transporters between species and have suggested that AEDs are either not substrates or are very weak supstrates of ABC transporters in humans[39]. Furthermore valproic acid, as possible strongest antiepileptic substrate of MRP2, is less effective in partial epilepsy than some other antiepileptic drugs; carbamazepine, lamotrigine, phenytoin, topiramate, etc[40,41] and have minimal effect in drug resistance in our group of patients.

The lack of association may be caused by overexpression of transmembrane proteins (MRP2, MDR1) in blood-brain barrier. Therefore, the overexpression of these transporters in epileptogenic tissue is likely to reduce the amount of drug that reaches the epileptic neurons and is also one plausible explanation for multidrug resistance in epilepsy[4].

Our results are in concordance with recent studies of Seo et al.[42], Kim et al.[43], and Kwan et al.[44] in which an association between the ABCC2 genotypes or haplotypes (including exon G1249A and exon C24T), and the responsiveness of AEDs was not found. Ufer M et al.[45] evaluated the association of non-response to antiepileptic pharmacotherapy with the frequency of variant alleles in the drug transporter genes ABCB1 and ABCC2 or in the CYP2C locus in young patients with epilepsy and an independent cohort of adults with drug-refractory epilepsy. Results of the study confirmed that ABCC2 24C>T genotype did not affect hippocampal ABCC2 expression, but was associated with increased ABCB1 expression, and in conclusion data suggest a higher risk of antiepileptic drug failure in ABCC2 24T allele carriers possibly because of compensatory upregulation of ABCB1. In all studies the main problem was uniform determining of drug resistance, small sample size and brain MRI positive etiology of epilepsy. Also in our study the main problem was small sample size.

In summary we did not identify significant association of ABCC2 gene polymorphisms 1249A>G and 24C>T with the development of drug resistance in patients with cryptogenic partial complex epilepsy.

REFERENCES

1. BROWNE TR, HOLMES GL, N Engl J Med, 344 (2001) 1145, DOI: 10.1056/NEJM200104123441507. — 2. KWAN P, BRODIE MJ, N Engl J Med, 342 (2000) 314. DOI: 10.1056/NEJM200002033420503. — 3. SPERLING MR, CNS Spectr, 9 (2004) 98. — 4. SISODIYA SM, Curr Opin Neurol, 16 (2003) 197. DOI: 10.1097/00019052-200304000-00013. — 5. BAČIĆ BARONICA K, MLINAC K, OZRETIĆ D, VLADIĆ A, KALANJ BOGNAR S, Coll Antropol, 35 (2011) 11. — 6. LOZIĆ B, PRIMORAC D, GLAVINIĆ R, KUZMANIĆ ŠAMIJA R, ZEMUNIK T, Coll Antropol, 35 (2011) 385. — 7. ŠMALCELJ A, SERTIĆ J, GOLUBIĆ K, JURČIĆ LJ, BRIDA M, Coll Antropol, 33 (2009) 933. — 8. TISHLER DM, WEINBERG KI, HINTON DR, BARBARO N, ANNETT GM, RAFFEL C, Epilepsia, 36 (1995) 1. DOI: 10.1111/j.1528-1157.1995.tb01657.x. — 9. SISODIYA SM, HEFFERNAN J, SQUIER MV, Neuroreport, 10 (1999) 3437. DOI: 10.1097/00001756-199911080-00032. — 10. DOMBROWSKI SM, DESAI SY, MARRONI M, CUCULLO L, GOODRICH K, BINGAMAN W, MAYBERG MR, BENGEZ L, JANIGRO D, Epilepsia, 42 (2001) 1501. DOI: 10.1046/j.1528-1157.2001.12301.x. — 11. SISODIYA SM, LIN WR, HARDING BN, SQUIER MV, THOM M, Brain, 125 (2002) 22. DOI: 10.1093/brain/awf002. — 12. ARONICA E, GORTER JA, JANSEN GH, VAN VEELEN CW, VAN RIJEN PC, LEENSTRA S, RAMKEMA M, SCHEFFER GL, SCHEPER RJ, TROOST D, Neuroscience, 118 (2003) 417. DOI: 10.1016/S0306-4522(02)00992-2. — 13. ARONICA E, GORTER JA, RAMKEMA M, REDEKER S, OZBAS-GERCEKER F, VAN VLIET EA, SCHEFFER GL, SCHEPER RJ, VAN DER VALK P, BAAYEN JC, TROOST D, Epilepsia, 45 (2004) 441. DOI: 10.1111/j.0013-9580.2004.57703.x. — 14. ABBOTT NJ, KHAN EU, ROLLINSON CM, REICHEL A, JANIGRO D, DOMBROWSKI SM, DOBBIE MS, BEGLEY DJ, Drug resistance in epilepsy: the role of blood-brain barrier. In: Mechanisms of Drug Resistance in Epilepsy: Lessons from Oncology (Wiley, Chichester, 2002), DOI: 10.1002/0470846356.ch4. — 15. SCHINKEL AH, WAGENAAR E, MOL CA, VAN DEEMTER L, J Clin Invest, 97 (1996) 2517. DOI: 10.1172/JCI118699. — 16. POTSCHKA H, LÖSCHER W, Epilepsia, 42 (2001) 1231. DOI: 10.1046/j.1528-1157.2001.01901.x. — 17. POTSCHKA H, FEDROWITZ M, LÖSCHER W, Neuroreport, 12 (2001) 3557. DOI: 10.1097/00001756-200111160-00037. — 18. POTSCHKA H, FEDROWITZ M, LÖSCHER W, Neurosci Lett, 327 (2002) 173. DOI: 10.1016/S0304-3940(02)00423-8. — 19. RIZZI M, CACCIA S, GUISO G, RICHICHI C, GORTER JA, ARONICA E, ALIPRANDI M, BAGNATI R, FANELLI R, D'INCALCI M, SAMANIN R, VEZZANI A, J Neurosci, 22 (2002) 5833. — 20. SILLS GJ, KWAN P, BUTLER E, DE LANGE EC, VAN DER BERG DJ, BRODIE

MJ, Epilepsy Behav, 3 (2002) 427. DOI: 10.1016/S1525-5050(02)00511-5. — 21. POTSCHKA H, FEDROWITZ M, LÖSCHER W, J Pharmacol Exp Ther, 306 (2003) 124. DOI: 10.1124/jpet.103.049858. — 22. KERB R, HOFFMEYER S, BRINKMANN U, Pharmacogenomics, 2 (2001) 51, DOI: 10.1517/14622416.2.1.51. — 23. SAITO S, IIDA A, SEKINE A, MIURA Y, OGAWA C, KAWAUCHI S, HIGUCHI S, NAKAMURA Y, J Hum Genet, 47 (2002) 147. DOI: 10.1007/s100380200018. — 24. MARZOLINI C, TIRONA RG, KIM RB, Pharmacogenomics, 5 (2004) 273. DOI: 10.1517/phgs.5.3.273.29831. — 25. CHOI JH, AHN BM, YI J, LEE JH, LEE JH, NAM SW, CHON CY, HAN KH, AHN SH, JANG IJ, CHO JY, SUH Y, CHO MO, LEE JE, KIM KH, LEE MG, Pharmacogenet Genomics, 17 (2007) 403. DOI: 10.1097/01.fpc.0000236337.41799.b3. — 26. DALY AK, AITHAL GP, LEATHART JB, SWAINSBURY RA, DANG TS, DAY CP, Gastroenterology, 132 (2007) 272. DOI: 10.1053/j.gastro.2006.11.023. — 27. HAN JY, LIM HS, YOO YK, SHIN ES, PARK YH, LEE SY, LEE JE, LEE DH, KIM HT, LEE JS, Cancer 110 (2007) 138. DOI: 10.1002/cncr.22760. — 28. NAESENS M, KUYPERS DR, VERBEKE K, VANRENTERGHEM Y, Transplantation, 82 (2006) 1074. DOI: 10.1097/01.tp.0000235533.29300.e7. — 29. HAENISCH S, MAY K, WEGNER D, CALIEBE A, CASCORBI I, SIEGMUND W, Pharmacogenet Genomics, 18 (2008) 357, DOI: 10.1097/FPC.0b013e3282f974b7. — 30. IZZEDINE H, HULOT JS, VILLARD E, GOYENVALLE C, DOMINGUEZ S, GHOSN J, VALANTIN MA, LECHAT P, DERAY AG, J Infect Dis, 194 (2006) 1481, DOI: 10.1086/508546. — 31. MOR-COHEN R, ZIVELIN A, ROSENBERG N, SHANI M, MUALLEM S, SELIGSOHN U, J Biol Chem, 276 (2001) 36923. DOI: 10.1074/jbc.M105047200. — 32. GUO SW, THOMPSON EA, Biometrics, 4 (1992) 361. — 33. SLATKIN M, EXCOFFIER L, Heredity, 76 (1996) 377. DOI: 10.1038/hdy.1996.55. — 34. EXCOFFIER L, LAVAL G, SCHNEIDER S, Evol Bioinform Online, 1 (2005) 47. — 35. REGESTA G, TANGANELLI P, Epilepsy Res, 34 (1999) 109. DOI: 10.1016/S0920-1211(98)00106-5. — 36. POTSCHKA H, LÖSCHER W, Neuroreport, 12 (2001) 2387. DOI: 10.1097/00001756-200108080-00020. — 37. POTSCHKA H, FERDOWITZ M; LÖSCHER W, Epilepsia, 44 (2003) 1479. DOI: 10.1111/j.0013-9580.2003.22603.x. — 38. WRIGHT AW, DICKINSON RG, J Pharmacol Exp Ther, 310 (2004) 584. DOI: 10.1124/jpet.103.064220. — 39. BALTES S, FEDROWITZ M, TORTOS CL, POTSCHKA H, LÖSCHER W, J Pharmacol Exp Ther, 320 (2007) 331. DOI: 10.1124/jpet.106.102491. — 40. KWAN P, BRODIE MJ, CNS Spectr 9 (2004) 110. — 41. KWAN P, BRODIE MJ, Seizure, 9 (2000) 464. DOI: 10.1053/seiz.2000.0442. — 42. SEO T, ISHITSU T, ONIKI K, ABE T, SHUTO T, NAKAGAWA K, J Pharm Pharmacol, 60 (2008) 631. DOI: 10.1211/jpp.60.5.0009. — 43. KIM DW, LEE SK, CHU K, JANG IJ, YU KS, CHO JY, KIM SJ, Epilepsy Res, 84 (2009) 86. DOI: 10.1016/j.eplepsyres.2008.12.001. — 44. KWAN P, WONG V, NG PW, LUI CH, SIN NC, WONG KS, BAUM L, Pharmacogenomics, 12 (2011) 319. DOI: 10.2217/pgs.10.183. — 45. UFER M, MOSYAGIN I, MUHLE H, JACOBSEN T, HAENISCH S, HÄSLER R, FALTRACO F, REMMLER C, VON SPICZAK S, KROEMER HK, RUNGE U, BOOR R, STEPHANI U, CASCORBI I, Pharmacogenet Genomics, 19 (2009) 353. DOI: 10.1097/FPC.0b013e328329940b.

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NEDOSTATAK POVEZANOSTI POLIMORFIZMA GENA ABCC2 I TERAPIJSKOG ODGOVORA NA ANTIEPILEPTIKE KOD BOLESNIKA SA EPILEPSIJOM U HRVATSKOJ

S A Ž E T A K

Usprkos napretku koji je postignut u medikamentoznom liječenju epilepsije, kod trećine bolesnika sa epilepsijom napadaji nisu zadovoljavajuće kontrolirani. Funkcionali utjecaj polimorfizma kod gena koji kodiraju transmembranske transportere može pridonijeti pojavi višestruke rezistencije na lijekove. Istraživanja rađena na ABCB1 genu pokazala su kontradiktorne rezultate. Dosadašnje studije govore da polimorfizam gena možda izravno ne uzrokuje promjenu u transportnoj aktivnosti P-glikoproteina (Pgp), nego bi mogao biti povezan sa jednom ili više varijanti u širokom području vezne neravnoteže, te može biti uzrokovan i višestrukim genskim polimorfizmom. Genski polimorfizmi se učestalo pojavljuju i u ostalim transmenbranskim transportnim sustavima uključujući protein multirezistencije na lijekove (MRP). Cilj ovog istraživanja je bio ispitati moguću povezanost polimorfizama gena ABCC2 G1249A eksona 10 i C24T eksona 1 sa razvojem rezistencije na lijekove. Ovo presječno istraživanje dio je farmakogenomskog istraživanja o epilepsiji u hrvatskoj populaciji, a koje je još u tijeku. Svi bolesnici koji su uključeni u istaživanje imali su postavljenu dijagnozu kriptogene parcijalne epilepsije sa ili bez sekundarne generalizacije, a bolovali su duže od dvije godine. Bolesnici su bili podjeljeni u dvije skupine. Prvu skupinu činila su 52 bolesnika refrakterna na trenutnu terapiju dok je drugu skupinu činilo 45 bolesnika sa zadovoljavajuće kontroliranim napadajima. Rezultati ove studije ne potvrđuju povezanost između genskog polimorfizma eksona 1 (24C>T) i eksona 10 (1249G<A) ABCC2 gena ili njihovog zajedničkog utjecaja na učinkovitost antiepileptičke terapije. Nije pronađena statistički značajna razlika u genotipski baziranoj analazi, frekvenciji alela, haplotipskoj ili kombiniranoj genotipskoj analazi.