GENETIC FACTORS AFFECTING THE DEVELOPEMENT OF ACUTE CORONARY SYNDROMES AND THE EFFECTIVENESS OF ANTIPLATELET DRUGS

Ph.D. thesis

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INTRODUCTION

The leading causes of mortality in the western countries are still the cardiovascular diseases, especially the ischemic heart disease (IHD) and the acute coronary syndromes (ACS). Approximatively sixteen million patients died because of cardiovascular events in 2001. Besides the classic cardiovascular risk factors genetic mutations are thought to have a role in the developement of the ACS. The positive family history and the ACS in the young underlies the importance of the genetics in the background of the ACS.

During the past decades acetylsalicilic acid, statins, ACE inhibitors and beta receptor blockers were shown to decrease mortality in the secondary prevention of IHD. Despite the more aggresive and effective therapy the cardiovascular mortality increased. New therapeuthic strategies were introduced to stop the increase of mortality. The new antiplatelet drug clopidogrel was shown to reduce mortality and morbidity in patients with ACS, however, severel studies reported uneffective antiplatelet therapy with either ASA or clopidogrel. In the background of the resistance to antipaltelet therapy the role of genetic factors were thought besides drug interactions, non-compliance etc.
My study focuses on the following genetic factors affecting the developement of ACS and the effectiveness of antiplatelet drugs:

1. Angiotenzine converting enzime (ACE) insertion/deletion (I/D) polymorfism

There is a insertion (I)/deletion (D) polymorphism in the 16 intron of the ACE gene, which affects the plasma ACE level. DD genotype represents a 2 fold increase in ACE level compared to II genotype. Controversial results have been reported in the setting of the role of ACE polymorphism in the developemnet of ACS.

2. Metilene tetrahydrofolate reductase (MTHFR) polymorfism

The patients homozigous to C-T mutation in the 677 position of the MTHFR gene have elevated homocistein level, which is a independent risk factor of IHD, stroke and periferal arterial disease. Some studies showed a correlation between the C-T mutation and IHD.

3. Glycoproteine (GP) IIIa platelet receptor PlA (A1/A2) polymorfism

PlA is a part of the GP IIb/IIIa membrane receptor family. The T-C mutation in the 1565 position of 2 exon of glycoprotein IIIa geneleads to PlA1 or A2 alleles. Recent datat suggest that PlA2 allele could be associated to the developement of ACS.

4. Mutations of lymfotoxin alfa (LTA) gene

Lymfotoxin alfa is a inflammational cytokin playing a key role in the iniciation of the local inflammational processes. As during the ACS local inflammation can cause the rupture of the unstable coronary plaque, the LTA can play a role in the iniciation of te ACS. Two mutations (LTA 1 and LTA3) were shown to related to the developement of ACS.

AIMS

The aims of our studies were to determine the possible role of the above mentioned mutations in the developement of ACS. We also studied the association between the PlA polymorphism and the resistance to ASA or clopidogrel.

RESULTS

1. PlA, ACE, MTHFR, LTA1 and LTA3 mutations in ACS patients

117 patients were PlA1/A1 (64 %) homozigous, 63 patients were A2 carriers. A2/A2 genotype was detected in 9 cases. There were significantly less A2 homozygous people or A2 carriers among healthy controlls.

There was no significant difference in the distribution of the ACE genotypes in the two populations.

MTHFR mutation appeared significantly more frequently in tpatients with ACS compared to controll population.

The prevalence of LTA1 és LTA3 polymorfisms was not significantly different in the two populations examined.

2. The possible association between PlA polymorphism and ASA resistance

ASA resistance was observed in 119 subjects (65 ACS, 30 ischemic stoke and 24 high-risk patients), while 166 (93 ACS, 39 stroke and 34 high-risk patients) showed an appropriate response to the ASA therapy. $Pl^{A2/A2}$ genotype occurred in ten subjects (8.4 %) with ASA resistance. We should note, that none of the patients with adequate ASA response was homozygous to the Pl^{A2} allele. The frequency of Pl^{A2} allele was significantly higher in subjects with ASA resistance than in the population showing normal response (0.21 vs. 0.14, $p<0.05$) to the drug. Pl^{A} genotypes were in Hardy-Weinberg equilibrium. Results of the adjusted logistic regression analysis show that genotypes containing A2 allele (A1/A2+A2/A2) are not an independent risk for ASA resistance (Odds ratio (95 % CI) of 1.04 (0.46-2.215), p=0.99).

3. Does glycoprotein IIIa gene (Pl^{A}) polymorphism influence the clopidogrel resistance

Clopidogrel insensitive platelet aggregation was observed in 38 subjects (19 with ACS, 14 with ischemic stoke and 5 with PAD), while 59 (18 with ACS, 23 with stroke and 18 with PAD) showed an appropriate response to the clopidogrel therapy. No significant differences could be found regarding the duration of the therapy between the responder and resistant patient groups (55 days and 59 days prior to the platelet aggregometry, respectively). $Pl^{A2/A2}$ genotype was revealed in one subject without clopidogrel resistance (2 %), in contrast none of the patients with clopidogrel resistance was homozygous to the Pl^{A2} allele. No significant difference in the prevalence of Pl^{A2} allele and the allele frequencies (PlA2: 0.09 vs 0.13) was detected, not even after adjusting for the concomitant medication and risk factors. Pl^{A} genotypes were in Hardy-Weinberg equilibrium. Our results show that the genotype containing an A2 allele

(A1/A2 or A2/A2) does not represent an independent risk factor for clopidogrel resistance.

SUMMARY

Our results support the hypothesis that some of genetic mutations could play a role in the developement of ACS. The Hungarian gene stock is different from other European populations, thus mutations described in the international literature should be examined in domestic population, as well, to prove their role in Hungary. The presence of Pl^{A2} allele (and especially the Pl^{A2} homozigosity) could affect the effect of ASA on platelet aggregation, but not the effect of clopidogrel. Our preliminary results suggest that patients with Pl^{A2} homozygosity might benefit from the administration of an ADP receptor antagonist (e.g., clopidogrel) rather than applying ASA.

PRACTICAL IMPLICATIONS

1. This is the first study confirming the role of Pl^{A2} allele in the developement of ACS in Hungarian population.
2. The MTHFR polymorfism could play a role in the formation of ACS.
3. We could not find any connection between ACS and ACE polymorfism.
4. There wasn't any relation between LTA1, LTA3 polymorfisms and the ACS.
5. Our results suggest that in case of ACS PlA and MTHFR polymorfisms should be considered instead of ACE, LTA1 and LTA3 mutations, in Hungarian population.
6. We found relationship between the occurence of Pl^{A2} allele and ASA resistance.
7. There wasn't any correlation between Pl^{A2} allele and clopidogrel resistance.
8. Further investigations are needed to be conducted to examine the genetic background of the clopidogrel resistance.
9. Our studies suggest, that the examination of PlA polymorfism should be considered in case of ACS, and clopidogrel should be administered instead of ASA in case of Pl^{A2} homozigosity.