TNF and ANXA2 gene polymorphism associated with outcome and coronary angiography features in patients with early acute coronary syndrome

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Background:
Genetic predisposition makes a considerable contribution to premature acute coronary syndrome (ACS) development. Tumour necrosis factor (TNF) is an important proinflammatory cytokine influencing intravascular inflammation. Annexin A2 (ANXA2) is an endogenous PCSK9 inhibitor. Higher LDL level is associated with AA genotype of ANXA2 gene SNP rs17845226.

Aim:
The aim of the study was to elucidate the association of TNF and ANXA2 gene polymorphism with coronary angiography features and outcome in patients (pts) with early ACS.

Methods:
We analyzed data from two prospective observational trials (2004-2007; 2014-2016) - 672 pts (498 men and 174 women) with premature ACS (men=55, women=60 years of age). Coronary angiography (CAG) data were analyzed in 225 pts. Genotyping of SNP rs1800629 of TNF (502 pts) and rs17845226 of ANXA2 gene (235 pts) was performed by RT-PCR with allele-specific primers. The primary endpoint was calculated as a combination of all-cause mortality, recurrent ACS, stroke, and peripheral vascular disease. We also analyzed recurrent coronary events (CE) (coronary deaths & recurrent ACS). The mean follow-up time: 414±347.6 days.

Results:
Mean age was 48.6±5.8 (M), 52.7±6.3 (F) years. 298 (44.3%) pts had STEMI, 362 (53.9%) pts - history of CAD, 500 (74.4%) - arterial hypertension, 32 (4.8%) - diabetes mellitus, 241 (37.1%) - heart failure (HF). The genotype distribution did not differ from the expected Hardy–Weinberg equilibrium: GG/AG/AA=0.557/0.191/0.006 (?=3.34, p=0.07) for TNF and CC/AC/AA=0.86/0.136/0.004 (?=0.05, p=0.82) for ANXA2. Carriers of allele A of TNF gene SNP had higher frequency of no significant coronary lesion (17.6% vs 5.9%; p=0.021) and NSTEMI (69.5% vs 50.8%, p<0.001). Carriers of allele A of ANXA2 gene SNP had higher frequency of coronary calcinosis (39.3% vs 19.6%; p=0.019) and HF (39.4% vs 22.3%, p=0.034). Carriers of A allele of TNF had higher frequency of CE (30.5% vs 19.5%, p=0.01, log-rank ?2=7.29, p=0.007). HF (OR, 2.686; 95% CI, 1.769-4.077; p<0.001), creatinine level (OR, 1.009; 95% CI, 1.001-1.017; p = 0.025) and carrying of A allele of TNF gene SNP (OR, 1.836; 95% CI, 1.163-2.898; p = 0.007) and STEMI at admission (OR, 1.009; 95% CI, 1.001-1.017; p = 0.025) were independent predictors of any unfavorable outcome and CE in a multivariable Cox regression model. LAD and left main
coronary artery involvement (OR, 1.836; 95% CI, 1.163-2.898; p = 0.007) was an independent predictor of any unfavorable outcome. Identified relationship was independent of invasive treatment of ACS.

Conclusion: Thus, in patients with early ACS TNF mediated inflammation is associated with NSTEMI, no significant coronary lesion and could play a significant role in the development of unfavorable outcome. Carrying of A allele of ANXA2 gene may accelerate coronary atherosclerosis in these patients and is associated with HF.