Cytokine Gene Polymorphisms (IL-6, TNFα) in Children with Rheumatic Fever in Latvia

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Introduction. Rheumatic fever (RF) is an inflammatory disease which follows group A streptococcal infection in children that present some genetic factors that predispose to the diverse clinical manifestations. Arthritis is the most frequent manifestation of RF, occurring in 75 % of patients, while 30–45 % develop rheumatic heart disease (RHD) as a result of valvular damage caused by the abnormal immune response (Guilherme, 2015). It is found that the development of autoimmunity in patients with RF/RHD is associated with genotypes of single- nucleotide polymorphisms (SNPs).

Cytokines are important secondary signals following an infection because they trigger effective immune responses. SNPs within the genes involved in the IL-6 and TNFα regulation are among the candidates to be studied in pathogenesis of RF. The most frequently studied polymorphisms – TNFα-308G/A is associated with mitral valve damage and TNFα-238G/A with myocarditis and aortal valve damage (Rajendranath, 2007). The data are different and Hernandez-Pacheco (2003) proved TNFα-238 as unrelated.

Aim, Materials and Methods. The aim of the study was to investigate the following cytokine gene SNPs – TNFα-238G/A(ra361525), TNFα-308G/A(rs1800795) and IL6-174G/C(rs1800795) in patients with rheumatic fever in Latvia.

DNA samples were obtained from 70 RF patients (born 1984–2002) and 254 healthy controls from the State Population Genome Database. To determine rs1800795 polymorphism was used real time TaqMAn SNP genotyping. Other polymorphisms were analyzed performing polymorphism-containing region Sanger sequencing. Statistical analysis was performed with Plink 1.06. All genotyped polymorphisms corresponded to Hardy-Weinberg equation, and initial SNP genotyping efficiency was over 98.8 %.

Results. Among 70 RF patients, 48 (68.5 %) were boys, 22 (33.4 %) were girls. Up to 7 years of age there were 23 (32.8 %) patients and after – 47 (67.1 %) patients. Acquired RHD developed in 47 (67.1 %) patients. Polyarthritis was diagnosed in 34 (48.6 %) patients. Analyzing TNFα genes, SNP of promoters in different clinical patients groups and comparing them with controls, statistically significant differences in the frequency of alleles were not observed, but in patients with polyarthritis IL-6 genes rs1800795 alleles showed statistically significant differences comparing with other clinical groups $p = 0.04737$, $OR = 0.4621$.

Conclusions.

1. Inflammatory cytokine IL-6 gene promoter's-174G/C position (rs1800795) polymorphism is polyarthritis development affecting in patients with RF in Latvia.
2. There was no proven link between TNFα-238G/A and TNFα-308G/A SNP and acquired heart disease development.