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Cytokine Gene Polymorphisms in Childhood Dilated Cardiomyopathy: Interferon- gamma, Tumor Necrosis Factor-alpha and Transforming Growth Factor - beta 1 Genes Are Associated with the Disease in Turkish Patients

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Dilated cardiomyopathy (DCM) is a cardiac muscle disease with reduced left ventricular systolic function[1]. Myocardial inflammation is the most common mechanism in the pathogenesis of cardiomyopathy in which cytokines may play an important role[2]. The objective of this study was to investigate the associations between tumor necrosis factor-alpha (TNF-α, -308), transforming growth factor-beta 1 (TGF-β1, +10, +25), interleukin-10 (IL-10, -1082, -819, and -592), interleukin-6 (IL-6, -174), interferon-gamma (IFN-γ, +874) gene polymorphisms and DCM.

Sixteen children with DCM (3 months-13 years) and 21 healthy controls were tested for the cytokine genes with polymerase chain reaction-sequence-specific primers (PCR-SSP). In our results, TNF-α (-308) A allele was higher in DCM (P=0.03). The frequency of TNF-α (-308) GG genotype (low expression) was significantly decreased in DCM (P=0.02). The children with DCM had significantly higher frequencies of IFN-γ (+874) TT genotype (high expression) and allele T while TA genotype (intermediate expression) was lower in patients (P=0.003, P=0.01 and P=0.04, respectively). Haplotype analyses showed that TT/GG and TC/GG ha plotypes of TGF-β1 (high expression) were significantly decreased while TC/GC, CC/GG and TT/GC (intermediate expression) haplotypes were increased (P=0.01 and P=0.04, respectively). There was no association between IL-6 and IL-10 genotypes/haplotypes and DCM (P>0.05).

TNF-α is a strong proinflammatory and immunomodulatory cytokine that intervenes inflammatory diseases and is produced by activated macrophages[3]. Frequency of TNF-α allele A was found high in DCM[4]. TNF-α allele A (-308) was found over-expressed in patients with end-stage non-ischemic myocardial dysfunction[5]. Tired et al did not find any association between TNF-α (-308) polymorphism and DCM[6]. In our study, allele A of TNF-α (-308) gene was found susceptible to DCM, while GG genotype of TNF-α (-308) showed a protective effect against the disease.

The production or activities of several cytokines are modulated by IFN-γ[7]. The AA homozygosity of IFN-γ (+874) T/A polymorphism was associated with poor prognosis in idiopathic DCM in older patients[2]. IFN-γ protected against the development of severe chronic myocarditis, pericarditis, and DCM after Coxackievirus B3 infection by reducing mast cell degranulation, and the profibrotic cytokines (IL-4, IL-1β, TGF-β1) in the heart[8]. In our study, the high expression of IFN-γ was found susceptible to DCM. We

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hypothesized that IFN-γ might play a possible role in the immuno-inflammatory process of childhood DCM, although it is not clear whether these act to preserve or protect against further inflammatory injury.

IL-6 is one of the proinflammatory cytokines with many systemic effects, including cardiovascular system[9]. The GG and GC genotypes of IL-6 (-174) are associated with increased levels of IL-6, while CC with decreased expression[10]. IL-6 levels were significantly associated with all outcomes of heart disease in adults[11]. IL-6 (-174) polymorphism was associated with LVESD and LVEDD in DCM[8]. Although allele C was higher in our patient group, there was borderline statistical significance between the groups (P=0.0590).

IL-10 is a regulatory cytokine which inhibits the production of IFN-γ and TNF-α and antagonizes the proinflammatory cytokine response[12]. The diagnosis of DCM has been associated with a reduction in IL-10 plasma levels, indicating its protective role in cytokine activation[13]. However, recent studies have suggested that IL-10 polymorphisms are not associated with DCM[2,4], in agreement with our results.

TGF-β1 is an anti-inflammatory cytokine that might play a major role in the immune modulation of heart function[6]. TGF-β1 expression is increased in the myocardium of patients with DCM[14]. TGF-β1 polymorphisms were correlated with better exercise capacity, and heart failure symptoms[2]. Tiret et al found no relationship between TGF-β1 gene polymorphism and DCM[6]. This study indicates that the high expression of TGF-β1 had a protective effect against the DCM, while intermediate expression had susceptibility to the disease. Fairweather et al reported that IFN-γ protected against the development of DCM after infection by reducing profibrotic cytokines like TGF-β1[8].

We conclude that the increase in the expression of IFN-γ and TNF-α genes may be associated with the etiopathogenesis of DCM; however, the increase in the expression of TGF-β1 gene may play a protective role against the development of this disease.

Key words: Cytokines; Dilated cardiomyopathy; Gene Polymorphism

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