ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Association of Interleukins Genes Polymorphic Markers with Speed of CGN's Advance.

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ABSTRACT

The authors investigated associations of polymorphism of interleukins genes (-511C/T *IL-1B*, -889C/T *IL-1A*, VNTR *IL-1Ra*, C-703T *IL-5*, T113M *IL-9*, -592C/A *IL-10*, -4257G/A *IL-13*) with nephritic survivance of the ill with chronic glomerulonephritis among 238 patients with CGN and 241 control group individuals. It is found that genetic variants 2R/5R, 4R/5R VNTR *IL-1Ra* are associated with accelerated hypotrophy of kidneys. The authors revealed factors reducing nephritic survivance. They are alleles -889C *IL-1A* and -592A *IL-10*, and arterial hypertension during CGN.

Keywords: chronic glomerulonephritis, accelerated hypotrophy of kidneys, nephritic survivance, genetic polymorphism, interleukins.

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ISSN: 0975-8585

INTRODUCTION

Nowadays chronic glomerulonephritis (CGN) is a serious problem for modern medical science because of disease's severity and high prevalence rate in different regions of the world [1]. It should be noted that the disease involves mainly active working aged persons, and that causes a significant social and economical damage [2].

Chronic glomerulonephritis is an allelically determined immune inflammatory disease [3], for progress of which, as shown in the literature, interleukins play an important role [4]. Interleukins genes are very diverse from the point of view of population. Some mutations in genes, which code corresponding interleukins, substantially change level of their expression, and that can have an impact on the progress of chronical inflammatory process [5].

Results of works dedicated to investigation of relations between interleukins candidate genes and advance of chronic glomerulonephritis are not identical for different populations. As aforesaid, in this work you can find estimation of the role of interleukins genetic polymorphisms (-511C/T *IL-1B*, -889C/T *IL-1A*, VNTR *IL-1Ra*, C-703T *IL-5*, T113M *IL-9*, -592C/A *IL-10*, -4257G/A *IL-13*) in accelerated hypotrophy of kidneys of patients with chronic glomerulonephritis.

MATERIALS AND METHODS

Interleukins genes polymorphisms analysis was carried out on the basis of the material of two sample groups: 238 patients with chronic glomerulonephritis and 241 control group persons aged 15-79 years old. The control group included individuals of Russian ethnicity, born in Central region of Russia and having no blood relationship among themselves. Patients were included to the illness group only after disease diagnosis ascertainment with the help of clinical and laboratory-instrumental examination technics. Clinical examination and diagnostics were performed by workers of nephrology department of Belgorod regional clinical hospital. Exclusionary criteria for the CGN group were diabetes mellitus (in anamnesis or found during the examination), hypertensive disease.

Nephritic survivance of persons with CGN was estimated in the group of 138 patients without end-stage renal disease. Among them 104 patients had unharmed functioning of kidneys (creatinine level was less than 140 mcM/l), 34 patients had chronic renal disease (creatinine level was more than 140 mcM/l during 6 months of observation). For analysis of nephritic survivance and influence of different factors on it we used the method of multiplicative estimators of Kaplan-Meier with Cox regression model [6].

We researched 7 polymorphic variants of interleukins genes (-511C/T *IL-1B*, -889C/T *IL-1A*, VNTR *IL-1Ra*, C-703T *IL-5*, T113M *IL-9*, -592C/A *IL-10*, -4257G/A *IL-13*), being of great importance for the progress of immune inflammatory diseases [7].

DNA was disengaged from peripheral blood via method of phenolic chloroform spirit extraction [8]. Analysis of all loci was performed via method of polymerase chain reaction (PCR) of DNA synthesis. Procedures and sequences of oligonucleotide primers and probes used are represented in works [9-12].

DNA markers genotyping was performed via methods of analysis of amplificated fragments lengths polymorphism (AFLP) (VNTR *IL-1Ra*), analysis of restriction fragments lengths polymorphism (-511C/T *IL-1B*, -889C/T *IL-1A*, C-703T *IL-5*, T113M *IL-9*, -4257G/A *IL-13*).

Associations of alleles and genotypes of investigated DNA-markers with speed of chronic glomerulonephritis advance were estimated wth the help of analysis of contingency tables 2x2 with calculation of criterion $\chi 2$ with Yates' correction for continuity and odds ratio (OR) with 95% confidence interval (CI). Analysis of associations of nephritic survivance with polymorphic genetic markers was performed via method of multiplicative estimators of Kaplan-Meier ("STATISTICA 6.0") [6].

ISSN: 0975-8585

RESULTS

We examined 238 patients with chronic glomerulonephritis and 241 control group persons. Main characteristics of examined group of patients with chronic glomerulonephritis and control group are shown in table 1. It should be noted that the CGN group level of arterial pressure and creatinine exceeded that of the control group ($p<0.001$).

During comparative analysis of frequencies of alleles and genotypes of investigated loci of interleukins among patients with CGN and the control group we revealed no statistically-valid differences (table 2).

Table 1: Characteristics of the subjects from the case and control groups

Characteristics	Cases	Controls
Total	238	304
Males	127 (53.4%)*	125 (51.86%)
Females	111 (46.6%)*	116 (46.64%)
Age, yrs	39.58 ± 14.58*	42.20 ± 6.28
Weight, kg	63.4 ± 2.1*	67.4 ± 1.7
Height, cm	165.4 ± 3.4*	168.6 ± 2.7
SBP, mm Hg	148.4 ± 26.5**	128.1 ± 4.4
DBP, mm Hg	92.7 ± 14.0**	82.2 ± 2.0
Creatinine, µmol/L	337.2 ± 44.1**	130.4 ± 7.8
GFR, ml/min	28,2±1,8	81,6±3,4

Note: *p>0.05; **p<0.001.

Table 2: Summary information about the studied polymorphisms.)

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				χ2	p
(-511) C/T *IL-1B*	Case	(-511)T *IL-1B*	33.84	0.01	>0.05
(-511) C/T *IL-1B*	Control	(-511)T *IL-1B*	35.21	0.87	>0.05
(-889) C/T *IL-1A*	Case	(-889)T *IL-1A*	28.03	0.21	>0.05
(-889) C/T *IL-1A*	Control	(-889)T *IL-1A*	32.06	0.89	>0.05
VNTR *IL-1Ra*	Case	*IL-1Ra*2*	25.13	0.75	>0.05
VNTR *IL-1Ra*	Control	*IL-1Ra*2*	21.84	0.11	>0.05
C-703T *IL-5*	Case	-703T *IL-5*	25.29	0.10	>0.05
C-703T *IL-5*	Control	-703T *IL-5*	28.48	0.98	>0.05
T113M *IL-9*	Case	113M *IL-9*	17.66	0.19	>0.05
T113M *IL-9*	Control	113M *IL-9*	18.67	0.36	>0.05
(-592) C/A *IL-10*	Case	(-592)A *IL-10*	27.73	0.24	>0.05
(-592) C/A *IL-10*	Control	(-592)A *IL-10*	22.67	0.41	>0.05
(-4257)G/A *IL-13*	Case	(-4257)A *IL-13*	27.93	1.53	>0.05
(-4257)G/A *IL-13*	Control	(-4257)A *IL-13*	23.90	0.93	>0.05

Notes: MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium. P values were calculated using the χ^2 test.

During estimation of nephritic survivance of patients with CGN, depending on genetic polymorphisms of interleukins, performed with the help of the method of multiplicative estimators of Kaplan-Meier, we found statistically-valid relations with progress speed for a locus *IL-1Ra*: individuals, which are carriers of genotypes 2R/5R, 4R/5R, tend to accelerated hypotrophy of kindeys (χ^2=8.29; p=0.05) (fig. 1).

For identification of factors having unfavourable prognostic value for CGN, we carried out a monofactor analysis of nephritic survivance with the help of Cox regression model. It was found that presence of allele -889C of gene *IL-1A* (p=0.05), allele -592A of gene *IL-10* (p=0.05) and arterial hypertension during CGN (p=0.01) declines nephritic survivance.

ISSN: 0975-8585

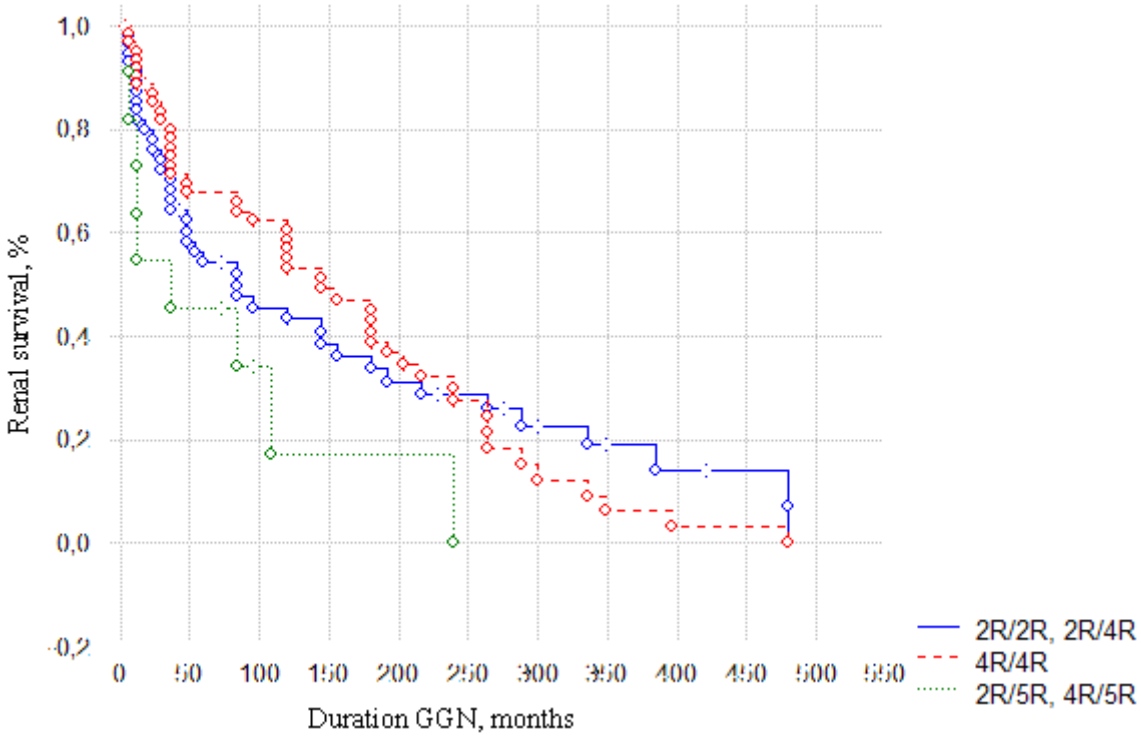

Figure 1: Renal survival of CGN patients with different genotypes of the VNTR polymorphism of the *IL-1Ra* gene.

SPECULATION

It was found that carriers of genotypes 2R/5R, 4R/5R VNTR *IL-1Ra* tend to accelerated hypotrophy of kidneys. The question of a functional significance of this polymorphism remains open. It is estimated that increase in repeats number promotes transcriptional activity of IL-1Ra. However, most of researches showed that decrease in production of *IL-1Ra*, having anti-inflammatory effect, leads to increase in production of *IL-1B* with anti-inflammatory effect [11,12]. Thus, this fact explains associations we found: accelerated hypotrophy of kidneys with genotypes 2R/5R, 4R/5R VNTR *IL-1Ra*.

We found factors declining nephritic survivance. Independent factors of risk are carrying of allele -889C of gene *IL-1A*, having anti-inflammatory effect, allele -592A of gene *IL-10*, having atopic effect, and arterial hypertension during CGN. These allelic variants (-889C *IL-1A*, -592A *IL-10*) are являются high-productive [10, 12, 13] and can cause more express pathogenetic effects of interleukin 10 (atopic effect) and interleukin 1A (anti-inflammatory effect) in an organism in the process of CGN advance.

RESUME

Thus, the work's results allow to judge molecular genetic markers 2R/5R, 4R/5R VNTR *IL-1Ra* to be factors of risk of accelerated hypotrophy of kidney during CGN. Factors declining nephritic survivance are carrying of allele -889C *IL-1A*, allele -592A *IL-10*, arterial hypertension during CGN.

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