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Genetic Aspects of Hcv Associated Arthritis: Evaluation of the Development and Clinical Course of the Disease

Shukurova Fazilat Narmamatovna[1], Karimov Marif Shakirovich[2], Parpibayeva Dinora Ayupovna[3], Eshmurzayeva Aida Abduganiyevna[1], Gimadutdinova Asiya Rinatovna[1]

[1]Department of Propaedeutics of Internal Diseases №2, Tashkent Medical Academy, Tashkent, Uzbekistan
[2]Head of Department of Propaedeutics of Internal Diseases №2, Tashkent Medical Academy, Tashkent, Uzbekistan
[3]Head of the Department of Simulation, Tashkent, Medical Academy, Tashkent, Uzbekistan

Abstract To study the nature of the association of IL-6 genotypes with the development and progression of the clinical course of associated arthritis (HCVaA) with viral hepatitis C. The study examined 52 patients with HCVaA in addition to a comparison group of 23 patients with chronic hepatitis C who had no signs of arthritis. IL-6 gene polymorphism was analyzed by polymerase chain reaction. The genotype C174G of the IL-6 gene in patients diagnosed with HCVaA is dominated by the genotypes of the G-allele, homozygous G/G and heterozygous C/G. Patients with HCVaA showed a decrease in the C/C genotypic variant of the IL-6 gene in the C174G genotype and an increase in the C/G genotypic variant compared to practically healthy people. The deterioration in the development and progression of the disease in patients with HCVaA is mainly associated with an increase in the heterozygous C/G variant. To predict the development and progression of HCVaA, it is necessary to determine the C174G polymorphism of the IL-6 gene.

Keywords HCV associated arthritis, Polymorphism of genes, C174G genotype of IL-6 gene

1. Introduction

To date, viral hepatitis C (HCV, HCV) is one of the most important medical and social health problems worldwide, and remains the main cause of disability and death. The World Health Organization estimates that approximately 150-170 million people are infected with hepatitis C virus (HCV) [1,2]. In addition to the primary effects manifested in the liver, chronic HCV infection can be associated with various extrahepatic manifestations (approximately 40-70%), such as arthralgia, arthritis, vasculitis, paresthesia, myalgia, itching, Sikki syndrome, cryoglobulinemia and glomerulonephritis. Studies have shown that the prevalence of joint syndrome associated with hepatitis C virus (HCVaA) is about 4-17% of patients with HCV. This is a small percentage, because many patients are diagnosed with a joint event only after consulting with a specialist. It is difficult to determine whether rheumatic symptoms, such as arthralgia and arthritis, occur due to a primary chronic HCV or HBV infection or due to a secondary process of rheumatic disease development [3,4]. Thus, the AIM of the STUDY was to study the nature of the relationship of IL-6 genotypes with the development and progression of the clinical course of associated arthritis (HCVaA) with viral hepatitis C.

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2. Materials and Methods

All examined patients were divided into 2 groups: group 1 - the main group – 52 patients with a positive response to HCV and observed associated arthritis, group 2 – the comparison group included 23 patients with HCV without associated arthritis. A study was conducted of 52 patients (average age - 38.54±6.00 years) diagnosed with chronic viral hepatitis C (HCV) who underwent initial consultation at the Department of Rheumatology at the Tashkent Medical Academy (TMA) and received inpatient treatment at the departments of the clinic of the Research Institute of Epidemiology, Microbiology and Infectious Diseases (NIIEMIZ) of the Republic of Uzbekistan. HCV-associated arthritis was registered in all patients. The diagnosis was confirmed by the presence of antibodies to HCV (anti - HCV) and HCV RNA by polymerase chain reaction (PCR). Gender distribution of the subjects of the research group: 30 men (M) and 22 women (F), average age 38.54±6.00 years. The comparison group included 23 patients with HCV without associated arthritis. Socio-demographic, clinical, laboratory and objective data were recorded using standardized questionnaires.

Patients who were diagnosed with heart failure, hypertension, diabetes mellitus, cancer, tuberculosis, other types of hepatitis, cirrhosis of the liver, severe renal insufficiency, with a history of NSAID intolerance, who received antiviral therapy for 6 months from the baseline for

HCV, with established diagnoses of systemic rheumatic diseases, pregnant women and carriers of the HIV virus were excluded from the study. All patients voluntarily gave written informed consent to participate in the study.

In our study, in order to analyze the significance of the polymorphism of the C-174G locus of the IL6 gene in the etiopathogenesis of HCV-associated arthritis, we conducted associative studies in 52 patients diagnosed with HCV and 23 patients with HCV-positive but undetected arthritis, as well as in 82 conditionally healthy donors of Uzbek nationality.

The samples of genomic DNA obtained from peripheral blood leukocytes of patients (52 patients with HCVaA in the main group and 82 in the control group) with an RNA/DNA extraction kit from the clinical material "Ampli Prime RIBOT prep" served as a material for studying the frequency of occurrence of single nucleotide substitution of the C-174G IL6 gene. To detect polymorphism of the IL6 gene, a polymerase chain reaction (PCR) was performed with a set of reagents to determine polymorphism C-174G of the IL6 gene. Studies of the C-174G polymorphism of the IL6 gene were carried out in the laboratory of the Department of Molecular Medicine and Cell Technologies of the Research Institute of Hematology and Blood Transfusion under the supervision of DSc, Professor A.T.Boboev. Using the "SNP-express" system, mutations (polymorphism) in the human genome were detected. Blood samples for PCR were collected in test tubes with EDTA VAC-CUETTE (Austria). Genomic DNA extraction from peripheral blood lymphocytes was performed by standard phenol-chloroform deproteinization with some modifications, as well as using RNA-sorb kits from InterLabService LLC and DNA-express blood from Litech LLC (Moscow) to determine polymorphism in the human genome C-174G of the IL6 gene according to the manufacturers' instructions. The quality of DNA samples was tested on a Nano Drop 2000 Thermo Scientific spectrophotometer (USA). Human genomic DNA isolated from whole blood leukocytes using the DNA-express-blood reagent was analyzed. Two amplification reactions are carried out in parallel with a sample of isolated DNA – with two pairs of allele-specific primers (Fig. 1).

3. Results and Discussion

Among the numerous genes whose products are involved in maintaining a stable state of health, the genes of cytokines, chemokines and growth factors produced by almost all cells of the body occupy an important place [5,6]. They have regulatory effects on the course of physiological processes (inflammation, sclerogenesis, angiogenesis, cell migration, proliferation, differentiation, tissue remodeling) [7]. To interpret the results of the study in HCVaA patients, it was necessary to assess the distribution of allelic and genotypic variants of the IL-6 gene polymorphism C 174 G in practically healthy individuals of the Uzbek population. In 82 practically healthy persons of Uzbek nationality (control group), the analysis of polymorphism C 174 G of the IL-6 gene showed the presence of the C allele in 19.5% of the examined, 71.5% had the G allele (Table 1).

It should be noted that the homozygous C/C genotype C 174 G of the IL-6 gene was detected in 3 (3.7%) of the examined practically healthy individuals, while the heterozygous C/G variant was found in 26 (31.7%). Homozygous G/G variant of this gene was observed in 53 (64.6%) persons of the Uzbek population. The data obtained indicate the predominance of the T allele, homozygous G/G and heterozygous C/G genotypes C 174 G of the IL-6 gene in the Uzbek population.

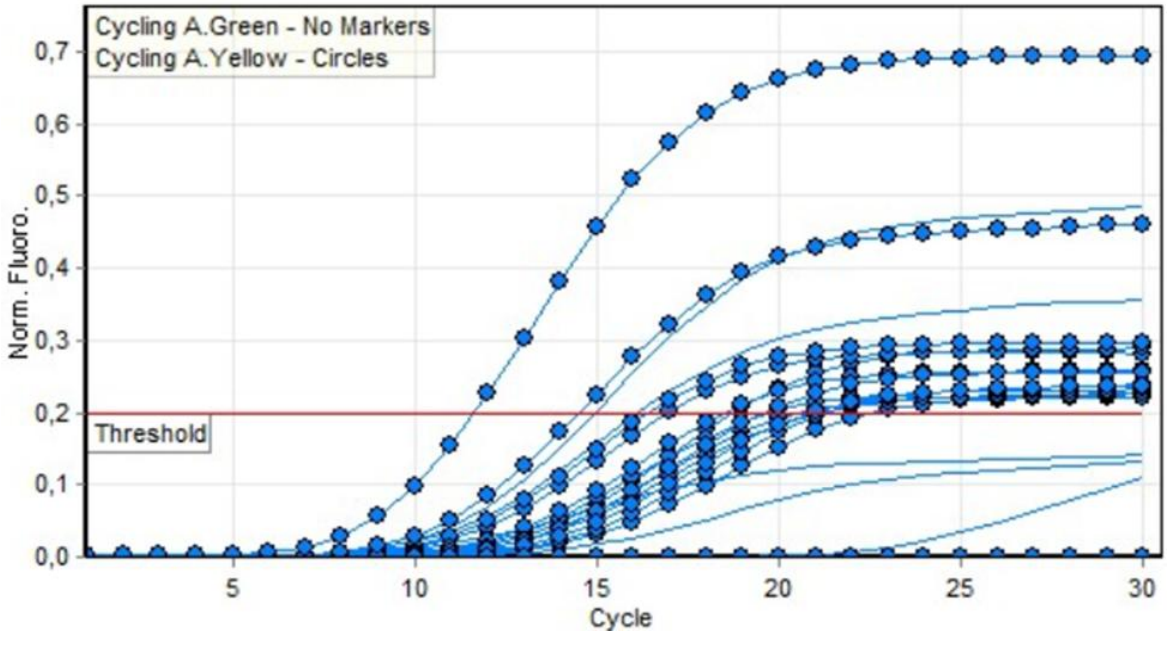

Figure 1

When analyzing the frequency distribution of alleles and variants of genotypes C 174 G of the IL-6 gene in 52 HCVaA patients, an increase in the C allele (up to 26%) was revealed against the background of an increase in the G allele to 74% ($\chi2$=0.7, p=0.4, OR=1.4) (Tables 1, 2 and 3). The distribution of genotypes of this cytokine in patients with HCVaA of the general sample showed a decrease in the homozygous C/C variant to 1.9% ($\chi2$=1.9, p=0.2, OR=4.9), while the heterozygous C/G variant was detected more often (in 25 patients or 48.1%) ($\chi2$=4.6, p=0.03, OR=2.2), and the frequency of the homozygous variant G/G was also detected more often - by 50% of patients. As can be seen from the data obtained, the frequency of distribution of alleles and variants of genotypes C 174 G of the IL-6 gene in HCVaA patients had its own characteristics. Thus, we can say that in this case, a high level of genetic variability is characteristic, which makes the analysis of the analyses analyzed by us more promising with the development of assimilated arthritis with HCV.

Table 3 presents the results of a comparative analysis of the distribution frequencies of alleles and genotypes of C-174G polymorphism in subgroups diagnosed with HCVaA and without arthritis. When analyzing the frequency distribution of alleles and genotypes of this locus in subgroups, there was a significant increase in the proportion of carriers of the negative C/G genotype in the subgroup of patients with arthritis (subgroup 1) compared with subgroup 2 (48.1% vs. 21.7%, respectively). At the same time, the ratio of the chances of detecting this allele was OR= 3.3, the relative risk of developing diseases was equal to RR= 2.2 at $\chi2$ = 4.6; p=0.03.

Table 1. The frequency of polymorphism of alleles and genotypes of the C 174 G locus of the IL6 gene in patients diagnosed with HCV and the control group

№	Groups	Frequency of alleles				Frequency distribution of genotypes					
		C		G		C/C		C/G		G/G	
		n	%	n	%	n	%	N	%	n	%
1	Main group n=75	36	24,0	114	76,0	3	4,0	30	40,0	42	56,0
1.1	HCVaA n =52	27	26,0	77	74,0	1	1,9	25	48,1	26	50,0
1.2	HCV without signs of arthritis n = 23	9	19,6	37	80,4	2	8,7	5	21,7	16	69,6
2	Control group n= 82	32	19,5	132	71,7	3	3,7	26	31,7	53	64,6

Table 2. Differences in the frequency of allelic and genotypic variants of C-174G polymorphism in the IL6 gene in the group of patients with HCV-associated arthritis and control

Alleles and genotypes	Number of alleles and genotypes examined				χ^2	P	RR	95% CI	OR	95% CI
	Main group n=75		Control group n=82							
	n	%	n	%						
C	36	24,0	32	19,5	0,9	0,3	1,2	0,80- 1,875	1,3	0,76- 2,231
G	114	76,0	132	71,7						
C/C	3	4,0	3	3,7	0,01	0,9	1,1	0,22- 5,251	1,1	0,21- 5,61
C/G	30	40,0	26	31,7	1,2	0,3	1,3	0,82- 1,92	1,4	0,74- 2,76
G/G	42	56,0	53	64,6	1,2	0,3	0,9	0,67- 1,12	0,7	0,36- 1,324

Table 3. Differences in allele frequencies and genotypic variants of the C-174G locus of IL6 gene polymorphism in patients with HCV-associated arthritis and in groups with undiagnosed signs of arthritis

Alleles and genotypes	Number of analyzed alleles and genotypes				χ^2	P	RR	95% CI	OR	95% CI
	1st subgroup n=52		2nd subgroup n=23							
	n	%	n	%						
C	27	26,0	9	19,6	0,7	0,4	1,3	0,67-2,593	1,4	0,616-3,373
G	77	74,0	37	80,4						
C/C	1	1,9	2	8,7	1,9	0,2	4,5	0,43- 47,39	4,9	0,417-56,48
C/G	25	48,1	5	21,7	4,6	0,03	2,2	0,96- 5,048	3,3	1,07- 10,32
G/G	26	50,0	16	69,6	2,5	0,1	1,4	0,948- 2,04	2,3	0,80- 6,475

The data obtained by us coincide with the results of observation by V.I. Konenkov et al.: among patients suffering from RA, cytokine genotypes associated with a low level of proinflammatory cytokine IL-10 together with a high level of proinflammatory cytokine IL-6 are most often found, which apparently moves the immunoregulatory balance towards active inflammation. According to a number of authors, this cytokine produced by macrophages actively initiates the initial phases of the development of the systemic inflammatory process and, as the disease develops, the dominant role in its maintenance passes to interleukin-6 [8].

And also, there were authors who noticed an increase in the level of IL-6 in RA and HCVaA [9]. Chung S.J. et al. significantly elevated levels of IL-6 in the serum of patients with RA were found, correlated with C-RB levels, and in patients with severe disease activity, it was noted that IL-6 and IL-11 concentrations decreased with improved symptoms. The authors concluded that these results indicate the involvement of IL-6 in the pathogenesis of RA, and the levels of IL-6 reflect the activity of the disease [10].

In this regard, we can say that cytokines play a significant role in the immune response to viral agents. Cytokines are key mediators of inflammation and joint destruction in HCVaA.

4. Conclusions

The results of our studied cases offer interesting assumptions about the role of cytokines in the pathogenesis of HCV associated with arthritis. Patients with chronic HCV infection and arthropathy had a higher level of the C/G genotype in the subgroup of patients with arthritis (subgroup 1) compared with the subgroup 2 (48.1% vs. 21.7%, respectively). Thus, the risk of developing associated arthritis with HCV in carriers of this genotypic variant increases 2.2 times. As can be seen from the data obtained, the development and course of HCVaA was associated with IL-6 genes mainly with a sharp increase in the frequency of heterozygous C/G variants and a decrease in the homozygous G/G variant.

REFERENCES

[1] Ott J.J., Stevens G.A., Groeger J., Wiersma S.T. Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine, 2012; 30 (12): 2212-9.

[2] Petruzziello A., Marigliano S., Loquercio G., Cozzolino A., Cacciapuoti C. Global epidemiology of hepatitis C virus infection: current data on the spread and spread of hepatitis C virus genotypes. J. Gastroenterol.2016; 22 (34): 7824-40.

[3] Palazzi C., D'Amico E., D'Angelo, S., Gilio M.; Olivieri I. Rheumatic manifestations of hepatitis C virus chronic infection: Indications for a correct diagnosis. World J. Gastroenterol. 2016, 22, 1405–1410.

[4] Sayiner Z.A., Haque U., Malik M.U., Gurakar A. Hepatitis C Virus Infection and its Rheumatologic Implications. Gastroenterol. Hepatol. 2014, 10, 287–293.

[5] Simbirtsev A.S. Cytokines: classification and biological functions // Cytokines and inflammation. – 2004. – T. 3, №2. – C. 16-22.

[6] Yoshida Y., Tanaka T. Interleukin 6 and Rheumatoid Arthritis // Biomed. Res. Int. – 2014. – Vol. 2014. – P. 698313.

[7] Nasonov E.L., Eliseev M.S. The role of interleukin 1 in the development of human diseases // Scientific-practical. rheumatol. – 2016. – vol. 54, No. 1. – pp. 60-77.

[8] Konenkov V.I., Zonova E.V., Leonova Yu.B. et al. Possibilities of using genotyping of cytokines with inflammation-regulating activity as biological markers for predicting the effectiveness of therapy for rheumatoid arthritis // Scientific-practical. rheumatol. – 2010. – №5. – C. 19-26.

[9] Riccio A., Postiglione L., Sabatini P., Linvelli M., Soriente, I., Sangiolo M.G., Amato P., Tarantino G. Similar serum levels of IL-6 and its soluble receptors in patients with HCV–related arthritis and rheumatoid arthritis: A pilot study. Int. J. Immunopathol. Pharmacol. 2012, 25, 281–285.

[10] Chung S.J., Kwon Y.J., Park M.C., Park Y.B., Lee S.K. The correlation between increased serum concentrations of interleukin-6 family cytokines and disease activity in rheumatoid arthritis patients.Yonsei Med. J. 2011, 52, 113–120.