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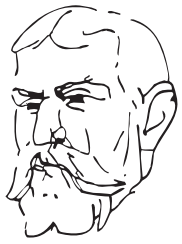

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ORIGINAL ARTICLE
PRACA ORYGINALNA

GENETIC POLYMORPHISM IN PATIENTS WITH EARLY AND LATE ONSET OF ULCERATIVE COLITIS

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ABSTRACT

The aim was to investigate SNPs of TLR-2,3,4, NOD2/CARD15, JAK-2, and IL-10 in patients with the early and late UC onset.

Matherials and methods: 126 patients with UC were investigated. To assess the predisposition of the early and late UC onset the incidence of the following SNPs: *Arg753Gln TLR2* gene, *Phe412Leu* TLR3 gene, *Asp299Gly* and *Thr399Ile TLR4* gene, *C-819T, G-1082A* and *C-592A* gene *IL-10*, *Val617Phe* gene JAK2, *Gly908Arg* gene NOD2/CARD15 were analyzed.

Results: 76 patients had early disease onset and 50 had a late one. SNPs of TLR3 were observed in 50.8% cases. TLR4 polymorphism was more common than TLR3, and was observed in 81 (64.3%) UC patients. Polymorphism of NOD2/CARD15 and IL-10 genes were revealed with almost the same frequency 49 (38.9%) and 50 (39.9%) patients, respectively.

Conclusions: Polymorphisms of TLR-2,3 genes and TLR4 Asp299Gly, NOD2/CARD15 prevailed in patients with the late UC onset that allows to suppose that bacterial flora plays one of the key roles in modification of immune response and UC development. In patients with early UC onset polymorphisms of the JAK2 and IL-10 genes prevailed responsible for the cytokine cascade activation and cause the immune mechanism that might lead to a more aggressive course of the disease.

KEY WORDS: ulcerative colitis; TLR-2,3,4; NOD2/CARD15; JAK 2; IL-10

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INTRODUCTION

Genetic analysis acquires an important role and might be pivotal in diagnosis, prevention and treatment of inflammatory bowel disease (IBD) in the nearest future [1, 2, 3]. Despite the upward trend in the incidence of ulcerative colitis (UC) at a young age, in recent years there has been revealed an increase number of patients whose UC onset happened in the second half of life (after 50 years). At a young age (20-35 years old), the peak of the incidence of UC is at the age of 20-22 years. The second peak of the disease is detected twice as often as the first, and it is diagnosed in elderly age of 50-55 years (late UC onset). The development of UC in patients with late onset is associated with the accumulation of predisposing and provoking factors (genetic predisposition, unfavorable environmental factors, eating disorders, allergization, medication[1, 2, 3, 4, 5] and determines the clinical features of UC: a greater hospitalization rate, an early need for steroid and immunosuppressive drugs compared with a group of young patients. The age-related features of the incidence of UC are associated with various factors (gender, place of residence, nationality, etc.), where genetic predisposition has the leading role [6, 7].

The predisposition to the development of UC is determined by the polymorphism of individual genes. NOD2/CARD15 assets nucleotide factor NF-κB, and induces transcription of tumor necrosis factor-α. The main role in genetic susceptibility to the violation of bacterial colonization is played by toll-like receptors (TLR). It is possible that TLR polymorphism in the intestine contributes to the formation of different types of response to bacterial antigens and affects the composition of the intestinal microbiota. Interleukin-10 (IL-10) is a key regulator of the immune response, the main anti-inflammatory cytokine. A correlation of single nucleotide gene polymorphisms (SNPs) in the promoter region of the IL-10 gene in positions –1082, –819 and –592, leads to a decrease in cytokine production and a predisposition to UC [2, 8, 9, 10, 11].

THE AIM

To investigate of SNPs of TLR-2,3,4, NOD2/CARD15, JAK2, and IL-10 in patients with early and late UC onset.

MATERIALS AND METHODS

126 patients with UC were investigated where during period (6 years). Informed consent was obtained from all patients before the start of the investigation. The most of patients with UC -62 (49.3%) had established diagnosis between 17 and 40 years (A2), and 52 (41.2%) patients had (A3), but only in 12 (9.5%) patients had diagnosis of UC was performed in childhood (Table I).

The location of UC characterized by the inflammation in the large intestine. Proctitis and proctosigmoiditis had 52 (41.3%) patients (E1) from left-sided UC suffered (E2) 32 (25.4%) persons and 42 (33.3%) patients had pancolitis (E3). Patients with moderate severity of UC also predominated among all UC patients – 52 (41.3%)

persons. Mild severity of disease occurred in 40 (31.7%) patients. Only 34 (27.0%) patients had severe UC. Index Mayo in all UC patients group consisted 2.6±0.9 score points. Severity of UC has correlated with extensive character of inflammation in the large intestine. As the majority of UC patients had moderate activity of disease, endoscopical index (EI) was equal to 2.1±0.5 in a whole group of patients with UC.

To assess the predisposition of the early and late onset of UC the incidence of the following SNPs: *Arg753Gln TLR2* gene, *Phe412Leu* TLR3 gene, *Asp299Gly* and *Thr399Ile TLR4* gene , *C-819T, G-1082A* and *C-592A* gene *IL-10*, *Val617Phe* gene JAK2, *Gly908Arg* gene NOD2/CARD15 were analyzed.

To highlight SNPs and used the polymerase chain reaction (PCR) technique DNA was extracted by the method of phenol-chloroform extraction, which was subsequently washed with 70% ethanol solution. After drying in air, further dissolution was carried out in deionized water, storage took place at a temperature of -20 °. Amplification of PCR sequences were carried out by thermocycler (Corbett, Australia), using the Litex (Russia) genotyping kits according to the instructions. To analyze the obtained amplification data, electrophoresis was used in a 2% agarose gel, which was stained with ethidium bromide, and a ultraviolet transilluminator was used for scanning. Characteristics of the studied polymorphic variants of genes were present in table II.

Table I. Clinical characteristics of UC patients

Disease	UC
Total number	126
Male/Female	1.3:1
Age of onset	
Mean (years)	48.3±9.2
Below 16 (A1)	12 (9.5%)
17- 40 (A2)	62 (49.3%)
Above 40 (A3)	52 (41.2%)
Location	
Distal colon (E1)	52 (41.3%)
Left-sided (E2)	32 (25.4%)
Pancolitis (E3)	42 (33.3%)
Severity (index)	Mayo
Total	2.6±0.9
Mild	40 (31.7%)
Moderate	52 (41.3%)
Severe	34 (27.0%)

RESULTS

Out of 126 patient 76 had early onset (before 35 years) and 50 patients had late onset of disease (after 50 years). Most of the patients had TLRs polymorphism. SNPs of TLR3 were observed in 50.8 % cases. TLR 4 (*Thr399Ile*) polymorphism was more common than TLR3, and was observed in 81 (64.3%) UC patients. At the same time, polymorphism of NOD2/CARD15 and IL-10 genes were revealed with almost the same frequency – 49 (38.9%) and 50 (39.9%) patients, respectively (Table III).

In patients with early onset of the disease TLR4 *(Thr399Ile)* and IL-10 polymorphism prevailed – 60 (78,94%) and 34 (44.73%) patients, respectively. In patients with late onset of the disease had significantly often polymorphism of TLR-2, 3 and 4 – 35 (70.0%), 33 (66.0%) and 25 (50.0%) patients, respectively. At the same time, there was a significant difference in the frequency of TLR2 gene polymorphisms in patients with early and late onset of UC (27.63% and 70.0%, respectively ($p<0.05$).

JAK2 and NOD2/CARD15 polymorphism was observed less common than changes in the TLR genes. At the same time, JAK2 polymorphism was more often detected in patients with early onset of UC 24 (31.6%), NOD2/CARD15 polymorphism prevailed in patients with late onset of the disease – 23 (46.0%) patients ($p <0.05$). The polimorphism of the IL-10 gene was more typical for patients with early disease onset 44,7% ($p <0.05$).

Despite the revealed differences in SNPs in different age categories of patients with UC, it should be noted that the average number of polymorphisms in one patient were not significantly different from patients with early to late onset disease, although it was slightly higher in patients with early onset UC (2,76 ± 0,13 ($p<0,1$)).

DISCUSSION

The association of NOD2/CARD15 gene polymorphism was the first with proven association with IBD [2, 12].Initially, the polymorphism of this gene, accompanied the development of Crohn's disease. However, recent studies have shown that polymorphism of the NOD2/CARD15 gene correlates with the development of UC. In our research it was revealed that NOD2/CARD15 SNPs are more common in patients with late onset of the disease that is corresponding with the other references [2, 13].This gene belongs to the family of pattern-recognizing receptors (PRR), which also include TLRs. Mutations in NOD2 presumably increases sensitivity to CD-receptors that can lead to changes in the immune response, the permeability of the intestinal mucosa barrier, causing the severety of disease.

TLRs are involved in the recognition of components of the cell wall of bacteria and viruses, in the activation of a cascade of protective mechanisms of local and systemic immunity [14]. TLRs are widely represented on the surface of the intestinal epithelium, on monocytes, macrophages [9]. The binding of receptors to a bacterial antigen leads to the activation of NF-kB and JAK2. JAK is involved in the phosphorylation of the membrane receptor, facilitating the coupling of STAT-proteins to the homologous domain of the phosphorylated cell membrane receptor. Phosphorylated STAT-proteins dimerize and translocate to the nucleus to regulate gene expression. Thus, the sequential cascade of phosphorylation leads to the activation of transcription factors, alters the expression of pro-inflammatory cytokines, and triggers the mechanism of the

Table II. Characteristics of the polymorphic variants of genes

Gen	Localisation	Polymorphism	Primer structure	Reaction fragment
TLR2	10q24.1-24.3 Ecson 5	Arg753Gln	5′-aat-tac-aac-cag-agc-ttg-gc 5′-tat-cac-ttt-cca-taa-aag-caa-g	SmaI
TLR4	10q24.3-qter 5′-flanking region	Asp299Gly	5′-cca-gtc-gag-tct-aca-ttg-tca 5′-ttc-att-ctg-tct-tct-aac-tgg	PstI
	10q24.3-qter Intron 6	Thr399Ile	5′-ctg-ctg-cta-atg-gtc-act-tg 5′-gga-gtt-caa-gac-cag-cct-ac	DraI
IL-10	C-819T	Deletion	5′-tgc-ttc-acg-tgt-tat-gga-ggt-tc 5′-gtt-ggg-ctc-aaa-tat-acg-gtg-g	-
IL-10	G-1082A	Deletion	5′-ggt-cat-tct-gaa-ggc-caa-gg 5′-ttt-gtg-gac-tgc-tga-gga-cg	-
TLR3	Phe412Leu	313AG	5′- gta-gtt-tgc-cca-agg-tca-ag 5′- agc-cac-ctg-agg-ggt-aag	BsoMAI

Statistical analysis was performed using the standard software package for statistical analysis MedStat.

Table III . SNPs in patients with late and early onset of UC

SNPs	Total, n = 126		Early onset, n = 76		p<	Late onset, n=50		p1<	p2<
	n	%	n	%		n	%		
Tlr2	56	44.4	21	27.6	0.05	35	70.0	0.05	0.05
Tlr3	64	50.8	31	40.7	0.1	33	66.0	0.05	0.5
Tlr4Asp299gly	45	35.7	20	26.3	0.05	25	50.0	0.05	0.05
Tlr4Thr399Ile	81	64.3	60	78.9	0.05	21	42.0	0.05	0.01
IL-10	50	39.9	34	44.7	0.1	16	32.0	0.1	0.0 5
NOD2/CARD15	49	38.9	26	32.9	0.1	23	46.0	0.1	0.05
JAK2	36	28.6	24	31.6	0.1	12	24.0	0.1	0.05
The average per patient	2,43±0,28		2,76 ± 0,13		0,05	2,11 ±0,32		0,05	0,05

p – differences between group of patients with early onset of UC and total group
p1 - differences between group of patients with late onset of UC and total group
p2 - differences between group of patients with early onset of UC and late oncet group

inflammatory response [2, 13]. TLRs activation promotes the synthesis of pro-inflammatory cytokines, including IL. TLR4 is found not only in the intestine, but also on cardiomyocytes, in the brain, on leukocytes in peripheral blood, TLR3 only on dendritic cells as the primary link in contact with the antigen. Thus, the violation of the pattern of the pattern-recognition domain TLR4 and the Asp299Gly Thr399Ile polymorphism are associated with the risk of UC [10]. TLR4 Asp299Gly gene polymorphism changes the resistance of a microorganism to Gram-negative bacteria, thereby contributing to the occurrence of dysbiosis. When single nucleotide substitutions appears in the TLR 2 gene, the susceptibility of the immune system to infectious agents changes. The significant difference between the frequency of gene polymorphisms TLR 4 was revealed our study: in patients with early onset prevailed polymorphism *Thr399Ile* TLR 4 gene, and in patients with late onset – *Asp299Gly* SNPs. At the same time, the difference in TLR3 polymorphism in patients with early and late onset was not significant. It should be noted that patients with late UC onset noted an increase in the frequency of polymorphisms of TLR genes except *Thr399Ile* gene TLR4 which is more character for young UC population [1, 9, 13].

Changes in these genes contribute to the violation of colonization and colonization resistance of the intestinal microbiota, which creates the basis for the formation of intestinal inflammation. On the other hand, the increased frequency of these polymorphisms were revealed in patients with late UC onset, thus, in the second half of life, which were not so common for patients with early UC onset. Consequently, we can assume the epigenetic effects of environmental factors on the gut microbiota formed on the background of long-term intestinal dysbiosis. This might lead to unspecific latent inflammatory process in the lamina propria with insensibly progredient modification of immune response and manifestation of UC in the elderly age.

It should be noted that the polymorphism of the IL-10 gene was more frequently detected in patients with an early onset of the disease, which could determine the relative insufficiency of the anti-inflammatory cytokine response in these patients [11, 15]. Based on the fact that the JAK2 system is involved in the synthesis of nuclear transcription factors and the formation of the immune response, including the expression of proinflammatory cytokines, the combination of JAK2 polymorphism and decreased synthesis of IL-10 can lead to a modified immune response

in the direction of enhancing the proinflammatory component that is observed in patients with early UC onset. In patients with late onset of UC the pattern recognizing receptor polymorphisms not only SNPs of TLRs genes, but also NOD2/CARD15 were dominant. This can change not only the presentation of the antigen, but also modify the formation of inflamasoma with a change in the differentiation of immunocompetent cells, stimulation of the pro-inflammatory component of the immune response in patients with late onset of UC.

CONCLUSIONS

SNPs were detected in patients with early and late onset of UC. The frequency of polymorphisms occurrence of individual genes was different. Polymorphisms of pattern-recognizing signal receptor TLR2, 3 genes and TLR4 Asp299Gly, NOD2/CARD15 prevailed in patients with late UC onset that allow to suppose that bacterial flora might play one of the key role in modification of immune response and contribute to the development of UC. In patients with early UC onset polymorphisms of the JAK2 and IL-10 genes prevailed responsible for the cytokine cascade activation and start the immune mechanism that might lead to a more aggressive course of the disease in such patients.

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This article is carried out within the framework of scientific research work: clinical and pathogenetic aspects of diagnostic and treatment of patients with a comorbidity diseases (cardiovascular, digestive, endocrine system), clinical and pathogenetic aspects.

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The Authors declare no conflict of interest

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