DOI 10.18019/1028-4427-2017-23-3-331-335

Personalized aspects of idiopathic osteoarthrosis of the hip joint

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Purpose To reveal personalized predictive criteria of idiopathic hip joint osteoarthritis development **Material and methods** The study included 100 unrelated patients with idiopathic hip joint osteoarthrosis in grade III–IV, aged 61.3 ± 8.5 years, ethnic Russians of Zabaykalsky Krai. Control group consisted of 100 patients of matching age (60±8.3 years), ethnic background and geographic area. Exclusion criteria were other types of osteoarthritis (post-traumatic, rheumatoid, etc.), acute inflammatory diseases and exacerbations of chronic conditions, and osteoporosis. Clinical, laboratory (polymorphism of genes determined for *TLR2-753Arg > Gln, TLR6-249Ser > Pro, FCGR2A-166His > Arg, DEFB1-52G > A, DEFB1-20G > A, TGFb1-25Arg > Pro, TNFα-308G > A, IL4-589C > T*) and radiogrpahy were employed in the study. **Results** Statistically significant differences between the patients with idiopathic coxarthrosis and control group were observed in carriers of -166Arg/Arg genotype of FCGR2A gene ($\chi 2$ – 99.2, $p < 0.0001$, OR – 255.2); -52A/A genotype of DEFB1gene ($\chi 2$ – 58.7, $p < 0.0001$, OR – 11.2); -20A/A genotype of DEFB1gene ($\chi 2$ – 42.2, $p < 0.0001$, OR – 8.3) and-589T/T genotype of IL4 gene ($\chi 2$ – 49.7, $p < 0.0001$, OR – 25.2). The detailed personalized analysis of the polymorphisms identified in coxarthrosis group showed an early onset and rapid progression of the disease (under 40 years of age) at a simultaneous carriage of 3 and 4 homozygous mutants in the studied polymorphisms, whereas carriage of 2 and over homozygous mutants in SNPs genes was not detected in the controls. **Conclusion** Identification of -166Arg/Arg genotype of gene FCGR2A, -52A/A genotype of DEFB1 gene, -20A/A genotype of DEFB1 gene, and -589T/T genotype of IL4 gene in residents allows for prediction of idiopathic coxarthrosis.

Keywords: idiopathic coxarthrosis, prediction, gene, polymorphism

INTRODUCTION

Coxarthrosis is the most common joint disease [1, 2]. In 60% of cases it leads to a decrease in working capacity and in 11.5% of cases to disability. Almost 80% of patients need primary arthroplasty of the joint. It indicates that this disease has a high medical and social importance as it is not only significantly worsens the patient's quality of life but also results in great socioeconomic costs [3, 4].

Anticipating the possible development of this disease and carrying out preventive measures if necessary is an important issue of modern medicine [5]. To date, many researchers are searching for markers of osteoarthritis development [6, 7, 8, 9, 10, 11]. Unfortunately, the "ideal" diagnostic index has not yet been revealed.

According to recent studies, the leading role in the development of diseases is assigned to hereditary factors. Genetically determined protein production has a significant effect on the development of a number of pathological conditions, including the development of osteoarthritis [11]. In view of the foregoing, identifying an association of a particular pathology with a certain genotype will ultimately allow the creation of a database (genetic passport) and timely implementation of the necessary prophylactic measures, thereby preventing the development of diseases and / or complications [12].

The **aim of the study** was to reveal personalized prognostic criteria for the development of idiopathic hip osteoarthritis.

MATERIALS AND METHODS

The study was conducted in accordance with the ethical principles of the Helsinki Declaration of the World Medical Association (the World Medical Association Declaration of Helsinki (1964, and 2011 amendments) and the *Rules of Clinical Practice in the Russian Federation* approved by the order of the ministry of health of the Russian Federation from June 19, 2003 No. 266.

Peripheral blood samples from 100 unrelated patients aged 61.3 ± 8.5 years with idiopathic osteoarthritis of the hip joint in stage III-IV, of Russian ethnic origin and living in the Trans-Baikal Territory who received high-tech medical care (total hip arthroplasty) in the traumatology de-

Miromanov A.M., Zabello T.V., Dorzheev V.V., Miromanova N.A., Emel'ianov A.S. Personalized aspects of idiopathic osteoarthrosis of the hip joint. *Genij Ortopedii*. 2017. T. 23. No 3. pp. 331-335. DOI 10.18019/1028-4427-2017-23-3-331-335. (In Russian)

partment of the Railroad Clinical Hospital at the station Chita-2 were a study object. The control group was 100 patients without any joint pathology of similar age (60 ± 8.3 years), nationality and residence area. Exclusion criteria were other types of osteoarthritis (posttraumatic, rheumatoid, gouty, etc.), acute and chronic inflammatory diseases in the exacerbation stage, and osteoporosis.

For genetic studies, the TLR2 point mutation at position 753 (Arg> Gln), the TLR6 mutation at position 249 (Ser> Pro), the FCGR2A mutation at position 166 (His>Arg), DEFB1mutation at position 52 (G>A), DEFB1mutation at position 20 (G>A), TGFb1mutation at position 25 (Arg> Pro), TNFα mutation at position 308 (G>A), and IL4 mutation at position 589 (C>T) were chosen. Amplification of the fragment of the investigated genes was carried out in a thermocycler Re Bis-M111 (OOO Bis-N, Novosibirsk, Russia) using the standard sets of primers of the scientific and production company Lytech-SNP (Moscow). Visualization of the amplification products was performed by electrophoresis in a 3% agarose gel with the addition of ethidium bromide in transmitted ultraviolet light [12].

The studies were performed when patients were admitted to the hospital. The data were processed using the Microsoft Office Excel 2010 and BIOSTAT software packages. To describe the nature of the distribution of quantitative characteristics and mean values (M), standard deviations (SD) were determined. For the group analysis for the qualitative binary feature, the χ^2 criterion was applied. To compare the quantitative indicators, the Mann-Whitney test was used. The risk of events was assessed by the odds ratio (OR) with a 95 % confidence interval (CI) calculated for it. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The distribution of genotypes carriage of the polymorphisms under investigation is presented in the table.

It was noted that not all investigated mutant genotypes had statistical significance of differences between the group of patients with idiopathic coxarthrosis and the control group: genotype -166Arg / Arg of the FCGR2A gene (χ^2 – 99.2, $p < 0.0001$, OR – 255.2); genotype -52A / A of the DEFB1 gene (χ^2 – 58.7, $p < 0.0001$, OR – 11.2); genotype -20A / A of the DEFB1 gene (χ^2 – 42.2, $p < 0.0001$, OR – 8.3); genotype -589T / T of IL4 gene (χ^2 – 49.7, $p < 0.0001$, OR – 25.2) (**Table**).

With a detailed personalized analysis of the composition of the revealed polymorphisms in the coxarthrosis group, it was revealed that with the simultaneous carrier of the 3 or 4 mutant homozygotes of the polymorphisms under study, the earlier onset of the disease (under 40 years old) and its rapid progression were noted while in the control group the carriage of 2 and more mutant homozygotes of the SNPs in genes studied was not identified.

It is found that FCGR2A (CD32) is included in the group of receptors for Fc - end of immunoglobulin G class. This receptor is localized on monocytes, granulocytes, eosinophils, macrophages and B lymphocytes, and facilitates interaction with immunoglobulins and, as a consequence, leads to the development of the response such as activation of macrophages, accompanied by the synthesis of cytokines and other biologically active molecules. Studies on the effect of polymorphism of FCGR2A gene (His166Arg) on the development of osteoarthritis were not found by us. However, it was noted that the combined carriage of genotype -166Arg / Arg of FCGR2A gene, genotype -159S / C of CD14 gene in patients with a flu AH1N1 led to its very fast progression and lethal outcome [13].

Recently, much attention has been paid to the study of the factors of innate immunity, in particular, to antimicrobial peptides, which include defensins. β-defensins have a broad spectrum of antibacterial, antiviral and antifungal activity, are involved in chemotaxis, in the induction of adaptive immunity, in the maturation of dendritic cells, etc. β-defensin 1 is encoded by the DEFB1 gene, which is located on the short arm of chromosome 8 at the 8p22-23 locus in the cluster of β-defensins. The polymorphism of the DEFB1 gene may be associated with the ß-defensin 1 production expressiveness at the mucous membranes level, therefore this polymorphism can explain the different susceptibility to diseases of infectious genesis [14].

It has been established that the polymorphic markers DEFB1 (-20G / A, -44C / G, -52G / A) are associated with a wide range of diseases (HIV-1infection, sepsis, infection caused by C. albicans, P. aeruginosa, etc.). Thus, it can be assumed that polymorphic markers can be associated with reduced (inferior) reactions of innate immunity due to defects in genes, which leads to a decrease in the expression of defensins and, thereby, contributes to a decrease in protection at the level of the mucous membranes and to the development of pathology [15].

Table

SNPs of the studied genes in the development of idiopathic coxarthrosis (χ^2)

Genotype	Control group (n=100)	Idiopathic coxarthrosis group (n = 100)	OR [95 % CI]	Outcome
SNP geneTLR2(Arg753Gln)				
Arg/Arg	65 (65 %)	84 (84 %)*	2.83 [1.44-5.55]	Favourable
Arg/Gln	35 (35 %)	16 (16 %)*	0.35 [0.18-0.69]	Favourable
Gln/Gln	–	–	1.0 [0.02-50.89]	Unfavourable
SNP gene TLR6 (Ser249Pro)				
Ser/Ser	4 (4 %)	9 (9 %)	2.37 [0.71-7.98]	Favourable
Ser/Pro	54 (54 %)	38 (38 %)	0.52 [0.3-0.92]	Favourable
Pro/Pro	42 (42 %)	53 (53 %)	1.56 [0.89-2.72]	Unfavourable
SNP gene FCGR2A(His166Arg)				
His/His	68 (68 %)	10 (10 %)*	0.05 [0.02-0.11]	Favourable
His/Arg	32 (32 %)	34 (34 %)*	1.09 [0.61-1.97]	Favourable
Arg/Arg	–	56 (56 %)*	255.2 [15.4-4223]	Unfavourable
SNP gene DEFB1(G52A)				
G/G	54 (54 %)	12 (12 %)*	0.12 [0.06-0.24]	Favourable
G/A	35 (35 %)	30 (30 %)*	0.8 [0.44-1.44]	Favourable
A/A	11 (11 %)	58 (58 %)*	11.2 [5.32-23.5]	Unfavourable
SNP gene DEFB1(G20A)				
G/G	52 (52 %)	19 (19 %)*	0.22 [0.11-0.41]	Favourable
G/A	36 (36 %)	28 (28 %)*	0.69 [0.38-1.26]	Favourable
A/A	12 (12 %)	53 (53 %)*	8.3 [4.0-17]	Unfavourable
SNP gene TGFb1(Arg25Pro)				
Arg/Arg	60 (60 %)	67 (67 %)	1.35 [0.76-2.41]	Favourable
Arg/Pro	28 (28 %)	25 (25 %)	0.86 [0.46-1.61]	Favourable
Pro/Pro	12 (12 %)	8 (8 %)	0.64 [0.25-1.63]	Unfavourable
SNP gene TNFα(G308A)				
G/G	73 (73 %)	73 (73 %)	1.0 [0.54-1.87]	Favourable
G/A	27 (27 %)	26 (26 %)	0.95 [0.51-1.78]	Favourable
A/A	–	1 (1 %)	3.0 [0.12-75.3]	Unfavourable
SNP gene IL4(C589T)				
C/C	73 (73 %)	29 (29 %)*	0.15 [0.08-0.28]	Favourable
C/T	25 (25 %)	37 (37 %)*	1.76 [0.96-3.24]	Favourable
T/T	2 (2 %)	34 (34 %)*	25.2 [5.86-108.7]	Unfavourable

Note: * statistical significance of the differences compared to the control group ($p < 0.05$)

It was shown that the presence of the homozygous genotype -589T / T in the IL4 gene is accompanied by a decreased production of IL-4 cytokine, which in turn contributes to the long-term maintenance of an increased content of pro-inflammatory cytokines, and, accordingly, to the progression of inflammation that inexorably leads to destructive processes in the tissues [16].

Prediction of idiopathic coxarthrosis is illustrated by the following clinical observations.

Clinical case 1 Patient I., 58 years old, hospitalized for selective surgery with a diagnosis of idiopathic right side coxarthrosis in stage III-IV, left side in stage III. NFS in grade I-II. Coxalgia on the right side (ICD-10 - M16.1) (**Fig. 1**). Concomitant diseases: atherosclerosis of the aorta, cerebral arteries, symptomatic hypertension. On admission the patient was studied for SNP in FCGR2A gene (His166Arg), SNP in DEFB1 gene (G52A), SNP of DEFB1 gene (G20A) and SNP in IL4 gene (C589T). It was established that the patient is a carrier of genotype -166Arg / Arg in FCGR2A gene, genotype -52G / A in gene DEFB1, genotype -20G / G in gene DEFB1 and genotype -589T / T in IL4 gene, which confirms our arguments on the impact of mutant homozygotes of the combinations studied in the development of coxarthrosis.

Clinical case 2 Patient D., 38 years old, was hospitalized for a planned surgical treatment with a diagnosis of idiopathic bilateral coxarthrosis in stage IV, NFS in stage III. Coxalgia was greater on the left (ICD-10 - M16.1) (**Fig. 2**). On the first day, the patient was tested on the SNP of the gene FCGR2A (His166Arg), SNP of the gene DEFB1 (G52A), SNP of the DEFB1 gene (G20A) and SNP of the IL4 gene (C589T). It was found that the patient was the carrier of 4 mutant homozygotes of the genes studied: the genotype -166Arg / Arg of the FCGR2A gene, the genotype -52A / A of the DEFB1 gene, the genotype -20A / A of the DEFB1 gene and the genotype -589T / T of the IL4 gene, which may indicate on the effect of three or more mutant homozygotes carriage for an earlier and rapidly progressing course of the disease.

Clinical case 3 Control group patient V., 50 years old, diagnosed with chronic calculous cholecystitis in remission stage, atherosclerosis of the aorta and cerebral arteries, symptomatic hypertension. No symptoms of joint damage syndromes were detected (**Fig. 3**). The study of the SNP of the gene FCGR2A (His166Arg), the SNP of the gene DEFB1 (G52A), the SNP of the gene DEFB1 (G20A) and the SNP of the IL4 gene (C589T) revealed only one mutant homozygote of the studied genes, the genotype -20A / A of the DEFB1 gene. This fact indicates a low predisposition to the development of coxarthrosis.

Clinical case 4 Control group patient M., 60 years old, was diagnosed with ischemic heart disease, progressive angina of tension in phase II cl. H2A, atherosclerosis of the aorta, cerebral arteries, symptomatic hypertension. No symptoms of joint damage syndromes were recorded (**Fig. 4**). In the study of the SNP of the gene FCGR2A (His166Arg), SNP of the gene DEFB1 (G52A), SNP of the gene DEFB1 (G20A) and SNP of the IL4 gene (C589T), the carriage of mutant homozygotes of the studied genes was not revealed.

Thus, the detection of -166Arg / Arg genotype in gene FCGR2A, genotype -52A/A in the gene DEFB1, genotype -20A/A in gene DEFB1 and the genotype -589T/T in gene IL4 in our residents might predict the development of idiopathic coxarthrosis which authorizes the possibility of carrying out prophylactic measures to prevent this socially significant disease.

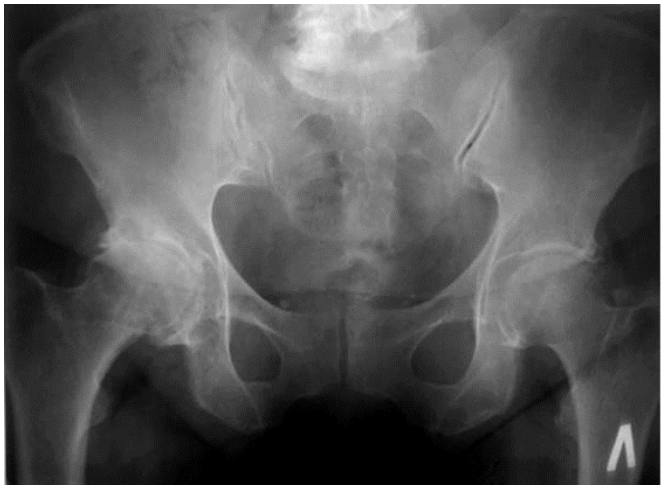

Fig. 1 AP Radiograph of the pelvis of the patient with idiopathic coxarthrosis in stage III to IV on the right side and in stage II on the left side

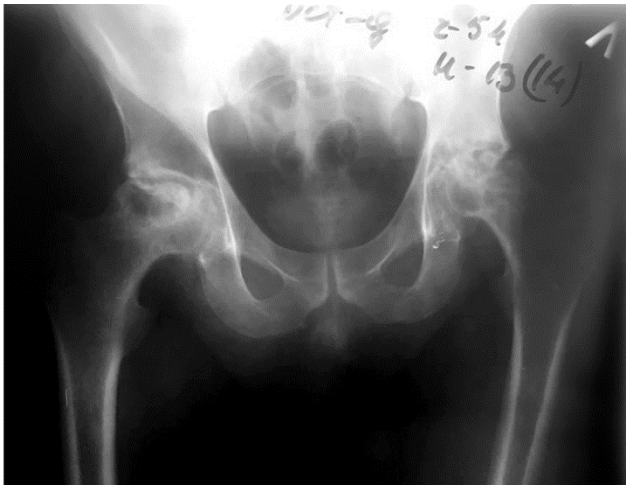

Fig. 2 AP Radiograph of the pelvis of the patient with bilateral idiopathic coxarthrosi in stage IV

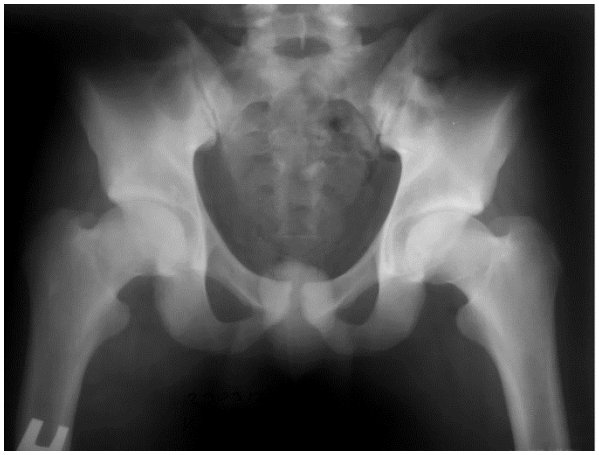

Fig. 3 AP Radiograph of the pelvis of the patient V. without any hip joint pathology

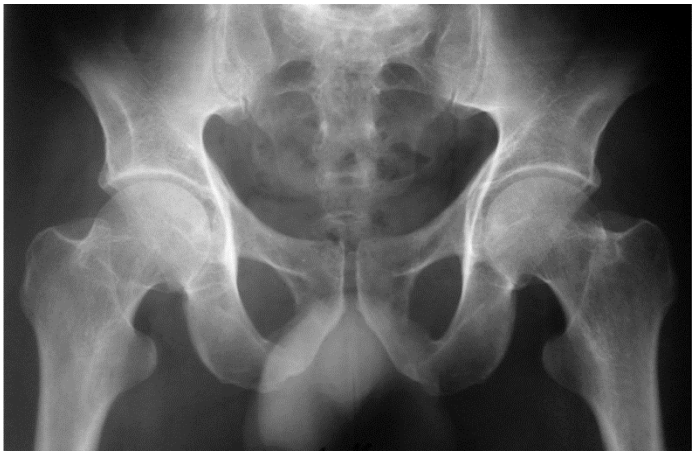

Fig. 4 AP Radiograph of the pelvis of the patient M. without any hip joint pathology

CONCLUSION

1. Determination of SNP in genes FCGR2A (His166A), DEFB1 (G52A), DEFB1 (G20A) and IL-4 (C589 T) allows for the anticipation of coxarthrosis development if at least two of their mutant homozygotes combinations are found.

2. If the carriage of three or more mutant homo-

zygotes of SNP in the genes FCGR2A (His166A), DEFB1 (G52A), DEFB1 (G20A) and IL-4 (C589 T) is detected, early and rapid progressioin course of idiopathic coxarthrosis might be expected.

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Received: 12.04.2017

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