diabetic nephropathy in type 2 diabetes - 3, hypertensive nephroangiopathy - 3, systemic diseases - 1, polycystic kidney - 1, urate nephropathy 1).

Indicators of platelet hemostasis in both groups were similar (in grams. A 276 ± 103 x 109 / l, c. B 265 ± 98 x 109 / l. The frequency of thrombocytopenia and thrombocytosis was small and comparable in both groups.

The average values of "routine" of hemostasis (TT, PT, INR, aPTT, PTI) did not deviate from the norm and were similar in both groups.

In group A greater intensity of activation of blood coagulation confirm increased the mean concentration of fibrinogen, whereas in group B such does not differ from the norm (the average level of fibrinogen in g B -. 4.07 ± 1,6g / l, g A -. 5, 09 ± 1,1 g / l (p = 0.004)), and a higher rate of hyperfibrinogenemia, identified in 2/3 patients in this group.

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The authors:

Popova Julia Alexeevna, graduate student, Medical Institute, "North-Eastern Federal University". Address: 677008, Republic of Sakha (Yakutia), Yakutsk, Kalandarishvili 38/5 sq. 27. Phone: 89142767120. E-mail: klausjuly@mail.ru;

Yadrihinskaya Vera Nikolaevna, Phypertinya, associate professor of "Hospital therapy, occupational diseases and clinical pharmacology Department", Medical Institute, "North-Eastern Federal University";

Krylova Maria Ivanovna, Phypertinya, senior lecturer of "Hospital therapy, occupational diseases and Clinical Pharmacology Department", Medical Institute, "North-Eastern Federal University";

Borisova Natalia Vladimirovna, professor of "Normal and pathology physiology Department", Medical Institute, "North-Eastern Federal University";

Petrova Palmira Georgievna, chief of "Normal and pathology physiology Department", Medical Institute, "North-Eastern Federal University";

Kardashevskaya Nadezhda Egorovna, 5th year student of the Medical Institute, «North-Eastern Federal University". Address: 677008, Republic of Sakha (Yakutia), Yakutsk, Lenina 56 sq. 9. Phone: 89243694511. E-mail: nadechek9437@gmail.com.

M.L. Khanzadyan, T.A. Demura, N.I. Duglas

GENETIC RISKS OF DEVELOPMENT OF PELVIC ORGAN PROLAPSE RECURRENCE AFTER HYSTERECTOMIES

ABSTRACT

Objective: to establish immunohistochemical and genetic markers of POP on the basis of studying of features of connecting tissue of women with a disease recurrence.

Materials and methods. The study involved 168 women, 134 of them with POP relapses aged 35 to 65 (96 after hysterectomy by vaginal access because of a total and partial uterus and vaginal walls prolapse). The control group consisted of 44 women aged 35-52 with no POP signs, after abdominal hysterectomy for uterine fibroids, adenomyosis, endometrial pathology.

Used: immunohistochemical (to assess tissue biopsies of sacrum-uterine and round uterine ligaments), the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs), genotyping by polymerase chain reaction of MMP/TIMP polymorphisms.

Results: Disturbances in the expression of the most important CT disorganization markers in POP shall comply with the expression of protein coding genes, in particular – MMPs and TIMP.

The results of studying the frequency of polymorphism genotypes in the groups of healthy women and those with POP are

presented in a chart.

Associations with GP development have been established among women with genetic polymorphisms: 5A5A (rs3025058) MMP3 gene. Statistical significance for the groups was preserved after the correction for multiple comparisons. The low frequency of CC allele of MMP2 gene (735 C>T) among patients with POP gave reason to consider it as a marker of biodegradation reduction in tissues connecting the core of pelvic organs.

The mutant CT allele of polymorphic variant rs 2277698 of TIMP-2 gene is more common among women with pelvic floor failure, but statistical significance was defined in relation to the protective CC genotype, revealed among half of healthy women.

Reducing of TIMP-1 accumulation on the background of metalloproteinases high expression indicates a substantial role of dynamic equilibrium violation in pathobiochemical disorders and pelvic dysfunction.

Conclusions. The determination of «risk» alleles predisposing to POP should be considered as a contribution to the understanding of the pathogenesis of the disease. They can be used as genetic markers of individual undifferentiated CT dysplasia manifestations.

Molecular and biological characteristics of tissue remodeling in POP allow us to consider immunohistochemical diagnosis as an improved capability of disease recurrence risk prediction after surgery and the choice of optimal treatment technology.

Keywords: pelvic organ prolapse, connective tissue dysplasia, collagen, extracellular matrix, matrix metalloproteinase (MMP), tissue inhibitors matrix metalloproteinase (TIMP), genetic polymorphisms.

INTRODUCTION

Pelvic organ prolapse (POP) is a serious medical and social problem among women of all ages, but mostly - in peri- and postmenopausal periods, with significant adverse consequences not only for health, but also for the quality of life, ability to work and social welfare. This problem is of high cost for the healthcare system as a whole [11]. POP incidence is believed to increase significantly in the coming decades due to the rapid growth of the elderly population in developed countries [19]. Delayed diagnosis of the disease is caused by the absence of any clinical manifestations of the pelvic floor insolvency among nearly two-thirds of patients with anatomical features of the pelvic descencia who happened to give birth [6]. According to the data acquired, only 40% of women aged 45-85 have objective POPevidence, but pelvic dysfunction symptoms, combined with incomplete emptying of the bladder and intestines, manifesting itself in the feeling of heaviness and the presence of a foreign body in the lower abdomen, urinary disorders and dyspareunia, were characteristic of only 12% of them [18].

Perennial discussion of etiological aspects and POPrisk factors contributed to the recognition of this disease being multifactorial. It was confirmed that the basis of pelvic failure is determined by anatomical and functional damage of phenotypically different tissues – supporting ligaments and striated muscles with prevailing changes in the connective tissue (CT) homeostasis [1,9]. The variety of CT functions, determining the active participation of its elements in a continuous renewal and restructuring in response to stress and damage, is regulated by hereditary, hormonal and metabolic factors [2]. CT morphogenesis dysregulation is initiated by genetic breakdowns that lead to the disruption of the formation of proteins' primary structure and extracellular matrix components [3,5]. Subsequently, it causes the destabilization of organ and tissue architectonics constituting the essence of dysplasia. Biological CT failure in cases of genital prolapse is reported to be formed as a result of qualitative changes arising because of collagen types I and III imbalance [11]. Protein metabolic disorder with enhanced lytic activity, decreased tensile strength, increased tissue extensibility, alongside with the reduction of another component of the extracellular matrix –elastin – were detected due to the study of the vaginal wall and supporting structures of the pelvic among patients with POP. All in all, this disease was indicated as a particular case of connective tissue dysplasia (CTD) [3,5]. Early detection of an imbalance in the CT structure, which plays an important role in maintaining the pelvic floor integrity, becomes possible due to identifying early signs of tissue degradation – violation of basic matrix protein correlation, altering protein properties and their morphogenetic functions. Remodeling of extracellular CT matrix by proteolysis or degradation of collagen fibers is performed by matrix metalloproteinases (MMPs) – extracellular family of zinc-dependent endopeptidases capable of destroying all kinds of extracellular matrix proteins [15]. Their involvement in tissue remodeling, angiogenesis, proliferation, migration and differentiation of cells, apoptosis, control over tumor growth proves to be regulated at several levels – nucleate, cell, tissue. It is known that MMPs include interstitial collagenase group (MMP-1, -2, -3) which cleave fibrillar collagen of corresponding types; gelatinases (MMP -2 and - 9) influencing amorphous collagen and fibronectin; stromelysins (MMP- 3, -10 and -11) affecting various components of the extracellular matrix including proteoglycans, laminin, fibronectin and amorphous collagen. The analysis of regulation of CT processes remodeling and the assessment of the role of matrix metalloproteinases (MMPs) involved in the degradation of extracellular matrix proteins remains the subject of scientific debates concerning POP pathophysiology.

The increase in MMP expression is connected with active remodeling of connective tissue structures – supporting ligaments of the uterus and vaginal walls, which promotes POPdevelopment. Specific MMP tissue inhibitors (TIMPs) perform the prevention of uncontrolled MMP excessive impact.

Considering the ideas about the genetic predisposition to the disease due to decreased activity of the enzymes involved in extracellular matrix formation and protein catabolism, the search for candidate genes as a missing link in biochemical conception of changes in the pelvic floor

structures becomes a significant trend in perineology [4]. Despite positive associative connections between individual genetic polymorphisms and the disease itself, general information about the genetic basis of POPappears to be haphazard and desultory.

Thus, the lack of comprehensive studies explaining the mechanisms of morphogenesis and pathological changes in the pelvic organs CT structures, with the detection of immunohistochemical and molecular genetic POPpredictors determines the prospects of suchlike analysis being aimed at reducing POPpostoperative recurrence.

OBJECTIVES OF THE STUDY

to establish immunohistochemical and genetic markers of POP on the basis of studying of features of connecting tissue of women with a disease recurrence.

MATERIALS AND METHODS

The study involved 168 women, 134 of them with POPrelapses aged 35 to 65 (96 after hysterectomy by vaginal access because of a total and partial uterus and vaginal walls prolapse).

The control group consisted of 44 women aged 35-52 with no POP signs, after abdominal hysterectomy for uterine fibroids, adenomyosis, endometrial pathology.

The study inclusion criteria: the presence of POP.

Exclusion criteria were malignant and autoimmune diseases.

The degree of genital prolapse was assessed by POP-Q classification (pelvic organ prolapse quantification), proposed by the International Continence Society (ICS) in 1996.

All women from the main and control groups had a comparable amount of parturition.

4 samples of tissue were obtained from 54 patients: right and left sacro-uterine ligaments, right and left round uterine ligaments. Sections were made on glass slides Menzel Super Frost Ultra Plus, covered with an adhesive; immunohistochemical (immunoperoxidase) reactions were conducted by the standard method with thermal antigen unmasking (Dako Protocols) and using the first antibody to MMP-1 and MMP-2 (LabVision, ready to use) and TIMP-1 (LabVision, 1:50).The results of immunohistochemical reactions was assessed semiquantitatively scored on a 6-point scale based on the percentage of stained cells or colored extracellular matrix and color intensity: 2 points – less than 20% stained ECM / cells, 4 points – from 20 to 40%, 6 points – 40 %.

Used: genotyping by polymerase chain reaction of MMP/TIMP polymorphisms with separation of DNA samples from whole blood.

Genetic polymorphisms of MMPs and TIMP were analyzed: MMP 2 rs2285053 (rs2285052) (735 C> T); MMP2 rs243865 (1306 C> T); MMP3 rs3025058 (1171 del> T [5A> 6A]); MMP9 rs3918242 (1562 C> T); MMP9 rs17576 (836 (855) A> G (Gln279Arg)); TIMP2 rs2277698 (303 C> T (Ser101Ser)). Genotypes were determined by PCR, with the curves of melting analysis by modified «adjacent probes» method (adjacent probes, kissing probes) using commercial test kits «SPA DNA-Technology», Russia. DNA for genotyping was taken from peripheral blood samples taken from EDTA as an anticoagulant with a set of reactants «Probe-GS-genetics» («SPA DNA-Technology», Russia). Oligonucleotide probes melting temperature was determined with the help of the detecting thermocycler DT-96 («SPA DNA-Technology», Russia).

Statistical result processing was performed using the program SPSS 13 for Windows.

χ2 criterion was used to determine the statistical significance of differences in the frequencies of alleles and genotypes in groups of patients. The distribution of genotypes for the studied polymorphic loci was tested for compliance to Hardy-Weinberg equilibrium. Statistical analysis of the results was used to calculate the frequency of genes, genotypes and their combinations occurrence, the odds ratio (OR) and 95% confidence interval (OR 95% CI). In assessing the reliability of the identified differences between the samples' average values and the reliability of the identified correlations p error probability was calculated. Differences at $p \leq 0,05$ were considered to be significant.At assessment of reliability of the revealed distinctions between average values of selections the probability of a mistake p (the importance paid off at $p \leq 0,05$) with the accounting of corrective action of Bonferroni.

RESULTS OF THE STUDY AND DISCUSSION

In round and sacro-uterine ligament samples of patients with POPMMP-1 and MMP-2 expression was observed in the form of lumps of brown staining in the extracellular matrix, ligament apparatus fibroblasts and the vascular endothelium. A similar trend was noticed in marker TIMP-1 imaging. Quantitative estimation of the average MMP-1 expression levels showed a higher content of stained cells and ECM among patients with POP compared to healthy women: 4±1,2

Distribution of genetic polymorphisms of MMP and TIMP on groups of healthy women and with POP

Gene	Polymorphismtype	Genotype	Frequency of genotypes				Criterion of distinctions Pearson's Chi-squared test	p	OR (CI 95%)
			Study group with POP		Control group				
MMP3	1171 del>T 5A>6A	5A5A	44	0,26	7	0,16	6,7	0,008*	2,6(1,3 -5,3)
		5A6A	91	0,54	20	0,45	6,3	0,01*	1,4 (0,7-2,8)
		6A6A	33	0,2	17	0,39	2,0	0,16	0,5 (0,2 –1,3)
MMP9	836/855 A>G	AA	80	0,48	23	0,52	4,3	0,6	1,2 (0,6-2,3)
		AG	68	0,4	14	0,32	1,3	0,96	1,5(0,7-2,9)
		GG	20	0,1	7	0,2	0,5	0,5	1,4 (0,5-3,6)
MMP9	1562 C>T	CC	73	0,43	25	0,57	2,5	0,11	1,7(0,9-3,3)
		CT	73	0,43	13	0,29	1,2	0,28	1,8(0,9-3,7)
		TT	22	0,13	6	0,14	0,01	0,92	1,0(0,4-2,8)
TIMP2	303 C>T 101 S	CC	59	0,35	23	0,52	4,3	0,04*	2,0 (1,0-3,9)
		CT	90	0,54	14	0,32	1,25	0,26	2,5 (1,2-4,9)
		TT	19	0,11	7	0,16	0,7	0,4	1,5 (0,6-3,8)
MMP2	735 C>T	CC	70	0,42	27	0,6	5,4	0,02*	2,2(1,1-4,4)
		CT	75	0,4	12	0,3	3,5	0,06	2,1(1,0-4,5)
		TT	23	0,1	5	0,1	0,16	0,7	1,2(0,4-3,5)

points to 2 ± 0,8 points (p <0,05).Index ofMMP-2 expression with POP(6±0,3 points) significantly exceeded the level of enzyme accumulation in the control group (4±0,5 points, p <0,05).

Other researches also show evidence of similarly increased MMP-1 and MMP-2 expression in the uterosacral ligaments and vaginal tissues among patients with POP. It corresponds to the predominance of extracellular matrix degradation in dysplastic morphogenesis. These results are consistent with ideas that MMPs and other proteases expression is not observed in healthy tissues and can be detected only in cases of remodeling, inflammation or high risk of postoperative disease recurrence.

The expression level of TIMP-1 (stained brown) appeared to be reduced in comparison with that in healthy women group: 1,5±0,5 points to 4±0,7 points, respectively (p <0.05).

The obtained data show MMP-1 expression increase among women with POP, alongside with reduced TIMP-1, compared with the control group, wherein the inhibitor deficiency remains unchanged regardless of age or menopausal status.

The results of numerous publications, despite some variability in the data due to the methodological aspects of various studies, indicate that abnormal metabolism of ECM proteins in the pelvic organs with the formation of an imbalance between the activity of MMPs and their inhibitors has a serious impact on various cell functions, including adhesion, migration, differentiation. Thus, MMP-1 and -2 can be considered as markers of collagen degradation. Disturbances in the expression of the most important CT disorganization markers in POPshall comply with the expression of protein coding genes, in particular – MMPs and TIMP.

The results of studying the frequency of polymorphism genotypes in the groups of healthy women and those with POP are presented in a chart.

It was stated that among MMP polymorphisms homozygote option 5A5A of MMP-3 gene (p=0,008; OR-1,5; CI 95% (0,7-2,9) was associated with increased POP risk, which proves its excessive effect on the destruction of collagen type I or biodegradable ability reduction.

The frequency of insertion-deletion polymorphism 1171 5A>6A, influencing the increased MMP3 gene expression, was much greater in groupwith POP(0.54 and 0.45).

6A6A homozygote frequency was much greater in the control group(0,4) (χ^2=2,0; p=0,16; OR-0,5; CI 95% (0,2-1,3), confirming its protective role in CT architectonics.

The low frequency of CC allele of MMP2 gene (735 C>T) among patients with POPgave reason to consider it as a marker of biodegradation reduction in tissues connecting the core of pelvic organs.

The heterozygous form CTof polymorphic variant rs 2285053 was found more frequently among women with pelvic floor failure, but showed no statistically important differences in the samples of patients with POPand healthy women (0,4 и 0,3).

The frequency of genetic MMP9 polymorphisms (1562 C>T) in the groups involved in our study did not differ significantly, despite the slight predominance of CT variant among patients with POP (0,43 and 0,3, p>0,05).

A polymorphic AG variant (locus rs 17576) of MMP9 gene (835/836) was bigger than its occurrence rate in the control group (0.4 vs. 0.32), but without any statistically significant differences.

The results obtained yielded to the data on the excessive biodegradable impact of MMP9 enzyme to collagen in the presence of the allele AG and GG in the study of Taiwanese scientists [16], but undoubtedly, the methodology of all scientific works presented on the subject should be taken into account.

The mutant CT allele of polymorphic variant rs 2277698 of TIMP-2 gene is more common among women with pelvic floor failure (0.54 and 0.32), but statistical significance was defined in relation to the protective CC genotype, revealed among half of healthy women (0.52) and only a third with POP(0,35) (χ2 = 4,3; p = 0,04; OR-2,0; CI 95% (1,0-3,9)).

The tendency to increase the activity of TIMP-2 enzyme in the presence of genetic determination causes the deficiency of molecular «protest» to the slowdown in progressive extracellular matrix degradation while considering CT protein synthesis retardation.

Reducing of TIMP-1 accumulation on the background of metalloproteinases high expression indicates a substantial role of dynamic equilibrium violation in synthesis processes, post-translational transformation and enzyme degradation in the tissues of the ligamentous apparatus – sacral and cross-uterine ligaments, indicating pathobiochemical disorders and pelvic dysfunction.

Conclusions. The determination of «risk» alleles predisposing to POP should be considered as a contribution to the understanding of the pathogenesis of the disease. They can be used as genetic markers of individual undifferentiated CT dysplasia manifestations.

Molecular and biological characteristics of tissue remodeling in POPallow us to consider immunohistochemical diagnosis as an improved capability of disease recurrence risk prediction after surgery and the choice of optimal treatment technology.

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The authors:

Khanzadyan Marina Laertovna - PhD, associate professor of obstetrics, gynecology and reproductive medicine Russian Peoples Friendship University; 117198, Russia, Moscow, ul. Maclay, 8. Tel. (495) 3214185, 89104445268, khmala@rambler.ru;

Demura Tatyana Alexandrovna - MD, Professor of Pathological Anatomy of academician A.I. Strukov Medical University First MGMU named after Sechenov, Moscow, Russia, 119991, st Trubetskaya. d. 8, demura-t@yandex.ru;

Duglas Natalia Ivanovna, MD, Head of the Department of Obstetrics and Gynecology, Medical University FPOV FGAOU HPE « Ammosov North-Eastern Federal University ", nduglas@yandex.ru.