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SOCIAL BURDEN AND GENETICS OF PELVIC ORGAN PROLAPSE

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Summary. Pelvic organ prolapse (POP) is a common disease affecting women. Despite the high prevalence of this disease very little is known about its etiology and pathogenesis. We speculated that *NAT2, GST T1* and *GST M1* polymorphisms might be a predisposing factor in the development of POP. Objective: To determine the correlation between *NAT2*, *GST T1* and *GST M* polymorphisms and POP.
Key words: pelvic organ prolapse, failure of the pelvic floor muscles.

Relevance. Pelvic organ prolapse (POP) is one of the most common pelvic floor pathologies [1,2,3,4,5,6]. There are a number of theories for the development of POP, but none of them fully explains the pathogenesis of the disease [2, 7,8,9,10,11,12]. Epidemiological data demonstrate the predominance of patients with POP among urban residents, which may indicate the influence of unfavorable environmental factors on the development of the disease [5,13,14]. It is known that a person's susceptibility to various diseases is determined by the so-called "predisposition" genes [1, 15,16,17], which include genes for detoxification system enzymes. Polymorphism of these genes, which is widespread in populations and changes the functional activity of the corresponding enzymes, determines the pathogenesis, course and effectiveness of therapy for various diseases, including gynecological ones [3, 18, 19,20,21].
N-acetyltransferase 2 (NAT2), being a phase II enzyme of the detoxification system, catalyzes the metabolic conversion of substances containing primary amino groups (NH2-) [4,22]. At the same time, NAT2 is involved in the metabolism of connective tissue, performing N-acetylation of carbohydrate components of the intercellular matrix of connective tissue (D-galactosamine and D-glucosamine) [8, 23,24,25]. The activity of the enzyme is determined by the polymorphism of the N-acetyltransferase 2 (NAT2) gene, which changes the functional activity of the protein [17]. Under conditions of low enzyme activity, the composition and spatial structure of protein-polysaccharide complexes, as well as their relationship with connective tissue fibers, change. On the other hand, non-metabolized NAT2 substrates are able to reduce the activity of copper-dependent lysyl oxidase, an enzyme that stabilizes the structure of collagen and elastin in the intercellular matrix of connective tissue [2, 26, 27, 28].

Since it is known that the smoking factor is recognized as independent in the development of POP [29], the study of the genetic characteristics of the enzyme systems involved in the detoxification of tobacco smoke components, namely, enzymes of the glutathione-S-transferase (GSTs) family, is of particular interest.

Enzymes of the glutathione-S-transferase family catalyze the addition of glutathione, the main cellular antioxidant, to the electrophilic center of a number of organic substances, leading to the formation of less toxic compounds [1,30].

The activity of enzymes of the GSTs family is genetically determined [1, 2]. The result of the deletion of both homologous genes of the GSTs family is the absence of the corresponding protein products, which may result in increased sensitivity of cells to pathological peroxidation of membrane lipids under hypoxic conditions.

The purpose. To determine the distribution pattern of polymorphic variants of the GST T1 and GST M1 genes in patients with PTO.

Material and methods. The study was carried out on the basis of the gynecology department of the perinatal center and in the Carmen and Lorastom clinics of the Bukhara region from September 2017 to July 2023. According to the purpose of the study, 66 patients from 25 to 82 years old with a history of 1 to 7 births suffering from various forms of prolapse. There were no isolated forms of anterior PTO in the studied cohort. All patients were examined by general clinical methods, with special attention paid to studying the condition of the pelvic floor. All patients were assessed for general and gynecological status using bimanual, manometric (perineometry), sonographic examination and vaginal palpation with determination of perineal muscle strength according to the Oxford scale.

The pelvic organ prolapse quantification (POPQ) system was used to determine the condition of the women's pelvic floor [1]. Molecular genetic analysis of DNA samples obtained by the standard method from peripheral blood lymphocytes was performed using the polymerase chain reaction (PCR).

Results. The average age of the patients was 51.7 ± 9.8 years. The distribution of genotypes for the GSTs and NAT2 genes was analyzed in two groups: mild (I–II) and severe (III–IV) POP severity. No significant differences were found in the frequencies of genotypes for the GST T1 and GST M1 genes in the clinical group and in the comparison group. Similar results were obtained when analyzing the distribution of GSTs genotype frequencies in POP subgroups of different stages. The “+”/“null” genotype ratio for the GST T1 gene varied depending on the stage of the disease from 2: 1 to 9.5: 1, while for GST M1 this ratio remained the same in all subgroups. No significant differences were found when comparing the frequencies of GSTs genotypes in the mild and severe POP groups. Results of the analysis of the frequency of genotype

combinations for the GST T1 and GST M1 genes in the clinical group and in the PTO group, no significant differences were found between the groups.

In severe PTO, a significantly higher frequency of combined "null" genotypes of GSTs was found than in the mild stage of the disease ($\chi^2 = 6.3$, $p = 0.01$).

When analyzing the NAT2 gene in the clinical group, a significant predominance of the genotype determining the slow type of N-acetylation was found ($\chi 2 = 4.1$, $p = 0.04$) compared to the population sample. Thus, in the PTO group, the genotype of “fast” N-acetylation was found in 36.4% (n = 24) of cases, “slow” — in 63.6% (n = 42), while in the population sample these values were 52.8% (n = 47) and 47.2% (n = 42), respectively. The ratio of “slow/fast acetylators” in the study group was 2:1, in the comparison group — 1:1. According to the calculated odds ratio, the presence of the genotype determining the slow acetylation type increases the probability of developing PTO by approximately 2 times (OR = 1.96 CI: 1.02–3.76). No reliable difference in the frequency of occurrence of “fast” and “slow” acetylators in the PTO group depending on the severity of the disease was found. In this case, the prevalence of "slow acetylators" was noted in the subgroup of stage I POP. The ratio of "slow acetylators" to "fast acetylators" in this subgroup was 4:1, while in the subgroups of stages II–IV POP this ratio was approximately 1:1. The data obtained in our study on the frequencies of genotypes for the GST T1 and GST M1 genes, as well as on the combinations of genotypes in patients with POP, corresponded to the indicators for the population sample and did not differ from the results of other studies [3]. At the same time, in the subgroup of severe POP, compared with mild disease, a high frequency of combined "null" genotypes of GSTs was revealed.

As is known, genetically determined pathologically low activity of enzymes of the GSTs family determines the susceptibility of cells to pathological peroxidation of membrane lipids under hypoxic conditions. We believe that damage to connective tissue cells, in particular, can lead to disruption of cell-matrix interactions and, accordingly, to decompensation of the mechanical properties of connective tissue, contributing to the development of pelvic organ prolapse.

The defect of the genes of the detoxification system in patients with POP that we noted suggests the role of exogenous factors, including environmental ones, in the pathogenesis of the disease. These data are confirmed by the results of studies demonstrating the predominance of patients with POP among urban residents [2].

The data obtained demonstrate a certain pathogenetic relationship between functionally weakened alleles of the genes of the GSTs and NAT2 detoxification system and clinical failure of connective tissue. In this case, the genotype of “slow” N-acetylation can be considered as an independent risk factor for the development of POP, while the double

"null" genotype for the genes of the GST family can be considered as an additional factor that aggravates the severity of the disease in "slow acetylators".

Conclusion. The genotype of "slow" acetylation is important for the formation of POP. In this case, the most unfavorable prognostic factor for the clinical course of POP is a combination of the "slow" genotype of NAT2 with a combined "null" genotype of GSTs.

Literature

1. Ward R.M., Velez Edwards D.R., Edwards T., Giri A., Jerome R.N., Wu J.M. Genetic epidemiology of pelvic organ prolapse: a systematic review // Am. J. Obstet. Gynecol. 2014. Vol. 211, N 4. P. 326-335.

2. Campeau L., Gorbachinsky I., Badlani G.H., Andersson K.E. Pelvic floor disorders: linking genetic risk factors to biochemical changes // BJU Int. 2019. Vol. 108, N 8. P. 1240-1247.

3. Weintraub A.Y., Glinter H., Marcus-Braun N. Narrative review of the epidemiology, diagnosis and pathophysiology of pelvic organ prolapse // Int. Braz. J. Urol. 2020. Vol. 46, N 1. P. 5-14.

4. Vergeldt T.F., Weemhoff M., IntHout J., Kluivers K.B. Risk factors for pelvic organ prolapse and its recurrence: a systematic review // Int. Urogynecol. J. 2018. Vol. 26, N 11. P. 1559-1573.

5. Khamdamov I.B. Experimental determination of the extensibility of the anterior abdominal wall tissues at different times of pregnancy using various approaches to hernioplasty// Academicia: An International Multidisciplinary Research Journal Vol. 12, Issue 04, April 2022 SJIF 2022 = 8.252 P.193-201 .

6. Khamdamov I.B. Improving tactical approaches in the treatment of hernias of the anterior abdominal wall in women of fertile age // New day in medicine. Bukhara, 2022.-№10(48)- P. 338-342.

7. Khamdamov I.B. Morphofunctional features of the abdominal press in women of reproductive age // New day in medicine. Bukhara, 2022.-№3(41)- P. 223-227.

8. Khamdamova M.T. Ultrasound features of three-dimensional echography in assessing the condition of the endometrium and uterine cavity in women of the first period of middle age using intrauterine contraceptives // Biology va tibbyot muammolari. - Samarkand, 2020. - No. 2 (118). - P.127-131.

9. Khamdamova M. T. Ultrasound assessment of changes in the endometrium of the uterus in women of the first and second period of middle age when using intrauterine and oral contraceptives // Биомедицина ва амалиёт журнали. – Ташкент, 2020. - №2. - 8 часть. - С.79-85.

10. Khamdamova M. T. Anthropometric characteristics of the physical status of women in the first and second period of middle age // A new day in medicine. Tashkent, 2020. - № 1 (29). - C.98-100.
11. Khamdamova M.T. Age-related and individual variability of the shape and size of the uterus according to morphological and ultrasound studies // News of dermatovenereology and reproductive health. - Tashkent, 2020. - No. 1-2 (88-80). - P.49-52.
12. Khamdamova M. T. Anthropometric characteristics of the physical status of women in the first and second period of middle age // Новый день в медицине. Бухара, 2020. - № 1 (29). - C.98-100.
13. Khamdamova M.T. Age-related and individual variability of the shape and size of the uterus according to morphological and ultrasound studies // News of dermatovenereology and reproductive health. - Tashkent, 2020. - No. 1-2 (88-80). - P.49-52.
14. Khamdamova M.T. Ultrasound features of three-dimensional echography in assessing the condition of the endometrium and uterine cavity in women of the first period of middle age using intrauterine contraceptives // Biology va tibbyot muammolari. - Samarkand, 2020. - No. 2 (118). - P.127-131.
15.Khamdamova M. T. Ultrasound assessment of changes in the endometrium of the uterus in women of the first and second period of middle age when using intrauterine and oral contraceptives // Биомедицина ва амалиёт журнали. – Ташкент, 2020. - №2. - 8 часть. - C.79-85.
16. Khamdamova M.T., Akramova D.E.Immediate and long-term results of surgical treatment of genital prolapse in elderly women// New day in medicine. Bukhara, 2025. – N3 (77). - P.201-206.
17. Khamdamova M.T., Khasanova M.T. Генетические механизмы развития гиперпластических процессов эндометрия у женщин в климактерическом возрасте // New day in medicine. Bukhara, 2025. – N3 (77). - P.207-211.
18. Khamdamova M.T. Individual variability of the uterus and ovaries in women who use and do not use various types of contraceptives // New day in medicine. Bukhara, 2020. - No. 3 (31). - P. 519-526.
19. Khamdamova M. T., Khasanova M.T. Генетические механизмы развития гиперпластических процессов эндометрия у женщин в климактерическом возрасте // New day in medicine. Bukhara, 2025.-№3(77)- P. 207-2011.
20.Khamdamova M. T., Akramova D.E. Immediate and long-term results of surgical treatment of genital prolapse in elderly women // New day in medicine. Bukhara, 2025.-№3(77)- P. 201-206

21. Khamdamova M. T., Umidova Nigora Nabi kizi. Genetic factors of genital endometriosis // New day in medicine. Bukhara, 2025.-№3(77)- P. 201-206H20.
22.Khamdamova M.T., Zhaloldinova M.M., Khamdamov I.B. The state of nitric oxide in blood serum in patients with cutaneous leishmaniasis // New day in medicine. Bukhara, 2023. - No. 5 (55). - pp. 638-643.
23. Khamdamova M.T., Zhaloldinova M.M., Khamdamov I.B. The value of ceruloplasmin and copper in blood serum in women wearing copper-containing intrauterine device // New day in medicine. Bukhara, 2023. - No. 6 (56). - P. 2-7.
24.Khamdamova M. T. Bleeding when wearing intrauterine contraceptives and their relationship with the nitric oxide system // American journal of pediatric medicine and health sciences Volume 01, Issue 07, 2023 ISSN (E): 2993-2149. P.58-62
25. Khamdamova M. T. The state of local immunity in background diseases of the cervix // Eurasian journal of medical and natural sciences Innovative Academy Research Support Center.Volume 3 Issue 1, January 2023 ISSN 2181-287X P.171-175.
26.Khamdamova M.T., Khasanova M.T. Various mechanisms of pathogenesis of endometrial hyperplasia in postmenopausal women (literature review) // New day in medicine. Bukhara. 2023. - No. 8 (58). - P. 103-107.
27. Khamdamova M.T. Reproductive Health of Women Using Copper-Containing Intrauterine Contraception // Eurasian Medical Research Periodical Volume 28 January 2024, ISSN: 2795-7624 .www.geniusjournals.org P. 39-45.
28. Khamdamov I.B. Advantages Of Laparoscopic Hernioplasty in Obesity Women of Fertile Age // Eurasian Medical Research Periodical Volume 28 January 2024, ISSN: 2795-7624 .www.geniusjournals.org P. 33-38.
29. Khamdamova M. T., Khasanova M.T. Genetic mechanisms of development of endometrial hyperplastic processes in women in menopacteric age // American Journal of Medicine and Medical Sciences 2025.- №15(2): P.372-375 DOI: 10.5923/j.ajmms.20251502.22
30. Blomquist J.L., Carroll M., Munoz A., Handa V.L. Pelvic floor muscle strength and the incidence of pelvic floor disorders after vaginal and cesarean delivery // Am. J. Obstet. Gynecol. 2020. Vol. 222, N 1. P. 62-65.