https://doi.org/10.48047/AFJBS.6.12.2024.1080-1085

African Journal of Biological Sciences
Journal homepage: http://www.afjbs.com
Research Paper Open Access

MODERN GENETIC ASPECTS OF PELVIC ORGAN PROLAPSE IN WOMEN OF REPRODUCTIVE AGE

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Article History
Volume 6 Issue 12, 2024
Received: 25 May 2024
Accepted : 25 June 2024
doi:
10.48047/AFJBS.6.12.2024.1080-1085

ABSTRACT
Background: Genital prolapse (GP) is a complex dynamic process that has a progressive course, accompanied by the development of structural and functional disorders in the body, often of a destructive nature. The relevance of the problem of genital prolapse is due to its prevalence, early manifestation and high frequency of relapses.
Purpose: A comprehensive study of the relationship between clinical and genetic aspects of the development of prolapse and dysfunction of the pelvic organs, prognosis, timely prevention and improvement of the quality of life of women.
Methods: The clinical section of the work was carried out on the basis of the Department of Obstetrics and Gynecology, Faculty of Medicine, Bukhara Medical University named after Abu Ali Ibn Sina, and genetic studies were carried out in the laboratory of the Institute of Genetics.
Conclusion: For women at risk for the development of genital prolapse with cervical injuries, it is recommended to determine the matrix proteins FBLN-5 and MMP-9 with additional genetic testing to determine further management tactics.
KEYWORDS: Genital prolapse, reproductive age, genetics, risk group.

INTRODUCTION

Despite the high prevalence of genital prolapse, the pathophysiology of this pathology has not been fully studied to date ( ). Some authors associate the “rejuvenation” of prolapse with the development of generalized connective tissue dysplasia ( ), minor forms of which occur with a frequency of 21.6% - 24.9% in women of reproductive age , and in perimenopausal women – 5.9% ( ).

At the same time, despite the high frequency of genital prolapse, only a few scientific studies have been described to study the pathogenesis of genital prolapse with cervical injuries, which are based on disorders of the elastic component of the connective tissue. The state of connective tissue (CT) of various structures of the pelvic floor largely determines the pathogenesis of the development of pelvic organ prolapse.

Elastic fibers allow tissue, under certain conditions, to stretch and elongate up to 70% of its length and, equally important, return to its original state, while damaged collagen fibers elongate only up to 4% ( ).

Based on these assumptions, Klutke J. et al. (2018) conclude that GP is based on a violation of the synthesis of elastic fibers, which play a leading role in maintaining the integrity of the pelvic floor. Fibulin-5 is a calcium-dependent elastin-binding protein that plays an important role in the formation of elastic fibers. The processes of degradation and proteolysis of collagen and elastic fibers of the extracellular matrix (ECM) occur with the participation of matrix metalloproteinases (MMPs). During the degradation of elastic fiber in the experiment, there was an increase in the activation of the expression of matrix proteinases in the altered tissues ( ). For example, the biological function of MMP-9 is associated with the degradation of collagen and elastin ( ).

Various researchers ( ) have conducted studies to study the genetic nature of HP. There are a number of genes and loci that can be considered as possible candidates involved in the pathogenesis of HP as a genetically determined pathology of a multifactorial nature. One of the key genes encoding elastic fiber assembly is the FBLN5 protein gene, which plays an important role in the development of HP ( ).

Considering the prevalence of genital prolapse with cervical trauma, the trend towards rejuvenation and the lack of highly effective long-term treatments, it is extremely important to study genetic mechanisms to prevent early manifestation and rapid progression.

The purpose of the study. Studying the role of enzymatic and genetic factors in the pathogenesis of genital prolapse with cervical injuries, to assess the degree of risk of developing the disease, early manifestation and rapid progression in women of reproductive age.

MATERIALS AND METHODS

During a gynecological examination, the stage of prolapse was determined pelvic organs according to the POP-Q classification. Patients of all three groups had 4 stage - complete prolapse of the uterus, as evidenced by the location of the points A and B at the level of +2 cm and below the hymenal ring on the anterior and posterior walls vagina, the total vaginal length (TVL) is reduced by no more than 2 cm. A comprehensive clinical examination of the patients was carried out, which included examination, gynecological and rectal examinations, laboratory (clinical and biochemical blood tests, coagulogram, blood group, Rh factor, RW, HIV, HbS, HCV, general urine analysis, bacterioscopic method to determine the vaginal microflora, cytological examination of ecto- and endocervix, aspirate from the uterine cavity) and instrumental methods studies (ultrasound of the pelvic and perineal organs before and after surgery, MRI, extended colposcopy), office hysteroscopy with simultaneous collection of material for morphological examination and hysteroscopy, separate diagnostic curettage of the endocervix, endometrium with availability of indications. Additional methods were performed according to indications research, depending on individual characteristics, extragenital pathology (electrocardiogram, function test external respiration, ultrasound examination of the vessels of the lower extremities and etc.), as well as consultations with other specialists (therapist, cardiologist, neurologist, urologist, etc.) if necessary.

RESULTS AND DISCUSSION

We studied the polymorphism of genes considered the most likely markers of PTO, namely: actinin-3 (ACTN3), matrix metalloproteinase genes (MMP9 and MMP12). MMP9 is a protease that is associated with the degradation of collagen and elastin in the extracellular matrix. An increased concentration of MMP9 leads to disruption of elastogenesis and disrupts the development of normal elastic fibers [11, 12]. In each group of patients, the ratio of the homozygous normal type of the MMP9 gene AA prevailed over the mutant GG. Noteworthy is the statistically insignificant but actual 2-fold increase in the number of patients with the homozygous mutant MMP9 genotype in the group with complete uterine prolapse in comparison with the incomplete variant of apical prolapse. When comparing the frequency of occurrence of recessive homozygotes between women from groups 3 and 1, this difference is even more pronounced, but is still not statistically significant in a small sample. This allows us to conclude that the recessive variant of the MMP9 gene polymorphism is not associated with the development of POP in patients, but may contribute to a more severe clinical course of prolapse. Undoubtedly, to clarify these circumstances, a larger sample of patients is required.

MMP12 is a macrophage metalloproteinase capable of hydrolyzing various proteins, including elastin and type 4 collagen. Increased expression of MMP12 leads to impaired elastic fiber strength [13]. When analyzing the polymorphism of the MMP12 gene, attention is drawn to the absence of homozygous mutant genes (GG) in the studied sample of patients with POP, but also the predominance of the homozygous normal type of polymorphism (AA) in the 1st and 3rd groups of patients. The heterozygous

genotype (AG) of the MMP12 gene was found 2 times more often in the group of patients with incomplete uterine prolapse than with a more severe form of prolapse. This allows us to conclude that carriage of the recessive allele G may play some protective role, slowing down the development of degradation of connective tissue structures during prolapse. Of course, with an increase in sample size, these results can be adjusted.

The total vector of forces influencing the human pelvic organs and contributing to their decline consists of the relatively constant force of gravity and the amplitude-changing force of intra-abdominal pressure. It is possible to resist the pushing of the pelvic organs through the lower aperture of the small pelvis only by joint and connected with another exposure to several anatomical devices. The pelvic organs are held in the correct position by complementary structures: the suspensory joints, fixing ligaments, the fascial apparatus of the pelvis and the muscular-fascial complex of the pelvic floor.

Together, normally, they successfully resist buoyancy forces, and a pelvic floor hernia does not form. If any of the listed devices is broken, the others

can compensate for this deficiency for some time, but with decompensatory degradation of the retaining structures, prolapse is inevitable. The duration of this subcompensatory stage, essentially the prodrome of POP, is largely determined by the structural, protein characteristics of the tissues and the biochemical characteristics of the restoration and degradation of these structures. This means that the search for genetic determinants not only of prolapse itself, but of the speed of its development, the duration of the prodromal stage of the disease is not only possible, but also necessary. Moreover, this is the only way to get closer to reliable prediction, high-quality prevention and effective timely treatment of POP in the full range of measures - from physiotherapeutic to surgical interventions.

The gene polymorphisms we studied were not chosen by chance: they reflect the structural and functional characteristics of the muscular (ACTN3) and connective tissue (MMP9, MMP12) compartments of the pelvic floor, as well as some compensatory mechanisms in response to ischemia (SOD2, CAT). The predominance of the normal variant of polymorphism when studying these genes in our study indicates the absence of obvious genetic determinants of the development of PTO. This is not surprising; POP is not a hereditary disease, but it may have a hereditary component in nulliparous women [16].

However, attention is drawn to the fact that the proportion of the mutant allele of the MMP9 gene increases in patients with severe forms of POP, and, on the contrary, the absence of recessive homozygotes GG

MMP12 gene in the studied sample. These coding features of metalloproteinases involved in connective tissue remodeling probably affect not only the risk of prolapse itself (the risk should decrease with pelvic organ prolapse (POP) when carrying the MMP12 GG gene), but also the risk of developing its severe forms (risk of severe forms should be increased when carrying the GG gene MMP9).

Another important finding was the significant predominance of the mutant allele of the actinin-3 gene (ACTN3) in patients with complete uterine prolapse. The muscular component of the pelvic floor is given unreasonably little attention, while it is these structures that dynamically resist the pushing, ever-changing force of intra-abdominal pressure. Based on our data, we can assume an increased risk of severe forms of prolapse or its more rapid development when carrying the TT genotype of the ACTN3 gene.

The least significant results were obtained when studying the enzymes of the antioxidant system, catalase and superoxide dismutase. The recessive allele T of the SOD2 gene and carriage of the recessive allele A of the CAT gene may have some protective effect on the development of severe forms of prolapse, slowing down the formation of the hernial orifice and/or hernial sac, probably delaying the development of severe forms of POP.

Despite the optimistic data regarding the search for genetic determinants of both POP itself and its severe stages, it should still be noted that there are no statistically significant differences between the studied groups. There may be several reasons for this. First, there is a small sample of women with POP. Secondly, diagnoses coded in the ICD as different nosological units are actually stages of the same process. This means that for further research it is necessary not only to expand the scope of the studies conducted, but also to use comparison groups in women with a comparable history, but not suffering from pelvic organ decline and NTD.

We believe that a closer look at the genetic predisposition to POP and its severe forms will help stratify women into risk groups and contribute to the concept of prognosis for this disease. This means that it will be possible to solve the problems of developing preventive measures, reducing the need for large volumes of surgical intervention and reducing the number of relapses of POP.

During the work, it was revealed that in the muscle biopsies of all patients there was no classical structure corresponding to the normal morphological picture of striated muscle tissue. The detected changes were of varying degrees of severity and consisted of quantitative and qualitative changes in muscle fibers, blood vessels and connective tissue components. The identified abnormalities in the structure of the pelvic floor made it possible to divide them into three types of pathomorphological pictures, which formed the basis for dividing the patients into three groups.

The first group included 30 (29.4%) patients with minimal structural abnormalities in the muscle tissue of the perineum; the second group included 45 (44.1%) patients with moderate pathomorphological changes in the m. levator ani, the third group consisted of 27 (26.5%) women with severe structural disorders in the tissues of the pelvic floor.

Minimal structural damage in m. levator ani were characterized by a greater number of vessels than normal, edema and lymphocytic infiltration of their walls and intercellular substance; the appearance of muscle dystrophy, proliferation of connective tissue. Moderate changes in the pelvic floor muscles were characterized by more pronounced muscle dystrophy, sclerosis of blood vessels, and proliferation of connective tissue that immured dystrophic muscle fibers.

Pronounced structural abnormalities in the muscle tissue of the perineum corresponded to pronounced vascular sclerosis, a decrease in their total number, atrophy of muscle fibers, and their replacement with connective tissue. When studying possible risk factors for POP, we did not find a correlation between the severity of pathomorphological changes in the perineal tissues and the number of births ($r = 0.10$, $p > 0.05$), genital prolapse in first-degree relatives ($r = 0.008$, $p > 0 .05$), body mass index ($r = 0.007$, $p > 0.05$) and causes of chronic increase in intra-abdominal pressure ($r = 0.13$, $p > 0.05$) (chronic constipation; persistent cough due to chronic diseases of the respiratory system and long-term smoking; physical activity associated with professional and household activities).

However, a correlation was found between the severity of structural abnormalities in the tissues of the pelvic floor and the presence of a history of obstetric perineal trauma ($r = 0.33$, $p > 0.05$), age at menopause (($r = -0.40$, $p > 0, 05$) and duration of postmenopause ($r = 0.51$, $p > 0.05$).

A comparison of pathomorphological changes with the severity of genital prolapse indicated a significant direct correlation between the severity of structural changes in the perineal muscles and the degree of dystopia of the pelvic organs according to all classifications studied.

The most severe forms of POP occurred in women with the most pronounced changes in the tissues of the pelvic floor. A significant increase in the perineal index in the groups was revealed, which indicates a more pronounced nature of disturbances in the architectonics of the perineum with increasing changes in the structure of the pelvic floor tissues ($r = 0.9$; $p < 0.05$).

Results of comparison of pathomorphological pictures with clinical manifestations of genital prolapse, assessed using various methods. The morphological picture and immunohistochemical study of collagen types 1, 3 and 4 in the perineal tissues taken during vaginal plastic surgery reflected the idea of structural changes in the perineal tissues, fully confirming the clinical picture.

In the absence of long-term exposure to additional risk factors for the development of pelvic floor incompetence (chronic increase in intra-abdominal pressure, condition of fatty tissue, features of blood circulation in the pelvis, concentration of sex steroids), regardless of the influence of a damaging factor (complicated vaginal birth), condition of muscle tissue perineum was characterized by the stage of compensation. The morphological picture practically corresponded to the norm: full-fledged muscle fibers without signs of dystrophy with a moderate amount of connective tissue and normal vessels that make up the intercellular substance. When conducting an immunohistochemical study, collagen was represented mainly by the most durable type 1, with the complete absence of type 4 collagen.

With continued exposure to numerous factors contributing to the development of genital prolapse, subcompensated changes occurred: swelling of the vascular walls and intercellular substance appeared with an increase in lymphocytic infiltration of the vascular walls. Initial signs of their sclerosis were noted; Muscle dystrophy developed, their functional activity decreased, and connective tissue grew, bridging the muscle fibers. The histochemical picture was characterized by a decrease in the content of type 1 and 3 collagen, and the appearance of a small amount of type 4 collagen, which is uncharacteristic of functionally active muscle tissue.

Subsequently, after a certain time, the process of decompensatory changes began in the tissues of the pelvic floor under the influence of ongoing and newly emerging factors (for example, a decrease in the production of sex steroids). At this time, pronounced vascular sclerosis developed, their total number

decreased, atrophy of muscle fibers developed, they were replaced by connective tissue, represented mainly by type 4 collagen. The concentration of collagen types 1 and 3 decreased significantly.

Thus, the tissues of the perineum underwent pathological changes over time according to well-known patterns: the stages of compensated, subcompensated and decompensated changes. Changes in the qualitative characteristics of collagen, identified using the immunohistochemical method of research, only confirmed this article.

The problem with the reliability of the results of such work is that it does not seem feasible to conduct a randomized controlled trial due to the impossibility of taking material from the perineal tissues of women with no disorders in this area. It is unlikely that the observed changes in the tissues will help reveal the etiology of prolapse, but a number of characteristic changes during the development of the pathology in question, reflecting compensatory processes in the tissues to varying degrees, can serve as a marker of the degree of neglect of the process. Thus, the disrupted unity of structural organization, functional consistency and morphological changes in the tissues of the perineum represents a pathogenetic cascade that develops in perineal incompetence syndrome.

The world literature presents various criteria for assessing the success of the results of surgical treatment of POP: improvement in the anatomy of the pelvic floor, resolution of symptoms, level of overall satisfaction with the results of treatment, reduction in the risk of recurrent prolapse and complications associated with a certain manipulation [6].

So, today there is every reason to assert that modern medicine, wandering in search of an optimal approach to the treatment of POP, has reached an ideological dead end. You can try to find a way out only with the only correct pathogenetic approach to any of the nosologies that the doctor encounters [4].

To summarize, in modern scientific literature the problem of scientific and technological development is presented quite widely, but a number of aspects remain controversial and poorly studied. Without studying the pathogenetic chain of failure of the pelvic floor muscles, namely the relationship between the biocenosis of the vagina, morphological changes in the vaginal wall and underlying tissues with NSTD, we cannot select a clear algorithm for timely diagnosis, select the optimal tactics for managing patients, and also reduce the number of relapses.

CONCLUSION

Thus, all women with POP exhibit pathomorphological changes in the pelvic floor, which worsen as pelvic floor incompetence and genital prolapse progress. Risk factors for increasing the severity of these changes are obstetric trauma to the perineum, early onset of menopause and a long postmenopausal period. The degree of pathomorphological changes in the perineum correlates with the stage of POP, assessed using any clinical classification, which makes it possible to indirectly judge the morphological picture of the perineum. To obtain more accurate ideas about the severity of pathomorphological disorders in the pelvic floor, it is necessary to take into account the identified risk factors. If they are present, the severity of genital prolapse should be considered more severe, which must be taken into account when choosing the optimal method of surgical correction of genital dystopia.

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