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REMODELING OF THE URINARY BLADDER DUE TO BENIGN PROSTATIC HYPERPLASIA

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According to the current protocols, treatment tactics in patients with benign prostatic hyperplasia is based on the activity of lower urinary tract symptoms, urodynamic parameters, and post void residual urine. At the same time, morphological changes in the detrusor remain without attention. The article presents data of the research the features of urinary bladder remodeling in patients with benign prostatic hyperplasia due to a long-term infravesical obstruction. 70 patients with benign prostatic hyperplasia in the stage of compensation, subcompensation and decompensation of the bladder were examined. According to the indications, the patients underwent prostatectomy, a biopsy of the anterior wall of the urinary bladder was taken. The study of morphological changes allows distinguishing three stages of urinary bladder remodeling in patients with benign prostatic hyperplasia: compensation, subcompensation and decompensation. As a result of prolonged infravesical obstruction in patients with benign prostatic hyperplasia, reverse, then irreversible morphological changes in the detrusor occur with the formation of urinary bladder rigidity. Substantiation of indications for surgical treatment in patients with benign prostatic hyperplasia, taking into account the morphological changes in the urinary bladder, makes it possible to prevent urinary bladder decompensation and related complications.

Key words: benign prostatic hyperplasia, morphology, urinary bladder, remodeling.

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РЕМОДЕЛЮВАННЯ СЕЧОВОГО МІХУРА НА ФОНІ ДОБРОЯКІСНОЇ ГІПЕРПЛАЗІЇ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ

Згідно з існуючими протоколами, тактика лікування хворих на доброякісну гіперплазію передміхурової залози базується на активності симптомів нижніх сечових шляхів, показниках уродинаміки та наявності залишкової сечі. При цьому морфологічні зміни в детрузорі залишаються без уваги. У статті наведено дані дослідження особливостей ремоделювання сечового міхура у хворих на доброякісну гіперплазію передміхурової залози внаслідок тривалої інфравезикальної обструкції. Обстежено 70 хворих на доброякісну гіперплазію передміхурової залози в стадії компенсації, субкомпенсації та декомпенсації сечового міхура. За показаннями хворим виконано простатектомію та взято біопсію передньої стінки сечового міхура. Вивчення морфологічних змін дає змогу виділити три стадії ремоделювання сечового міхура у хворих на доброякісну гіперплазію передміхурової залози: компенсацію, субкомпенсацію та декомпенсацію. Внаслідок тривалої інфравезикальної обструкції у хворих на доброякісну гіперплазію передміхурової залози відбуваються зворотні, а потім і незворотні морфологічні зміни в детрузорі з формуванням ригідності сечового міхура. Обґрунтування показань до хірургічного лікування у хворих на доброякісну гіперплазію передміхурової залози з урахуванням морфологічних змін сечового міхура дає змогу запобігти декомпенсації сечового міхура та супутніх ускладнень.

Ключові слова: доброякісна гіперплазія передміхурової залози, морфологія, сечовий міхур, ремоделювання.

The study is a fragment of the research project "Clinical and pathogenetic characteristics of urinary tract remodeling in the elderly and senile people", state registration No. 0120U104459.

Transurethral resection of the prostate (TURP) remains the "gold standard" for the benign prostatic hyperplasia (BPH) surgical treatment [11]. At the same time, F. Fusco et al. (2017) note that in the early and late postoperative period, 5–35 % of patients had lower urinary tract symptoms (LUTS) [3]. M. Speakman et al. (2015) note a direct relationship between LUTS after surgery and the amount of post void residual urine (PVR) before surgery [10].

Over the past 30 years, there has been a persistent towards drug therapy – only 10–15 % of patients with BPH have surgical treatment [9]. A. Morton et al. (2020) proved that the persistence of LUTS in patients with BPH in the postoperative period is associated with an unjustified delay in surgery. According to clinicians, this indicates the imperfection of treatment standards [7]. According to the EAU recommendations, indications for surgical treatment are based on the international prostatic score scale (IPSS≥20 points), urodynamic parameters (Q_{max}<12 mL/s), presence of PVR>200 ml. In 2018, the AUA updated the recommendations, expanding the indications for surgical treatment of patients with BPH in the presence of any of the following factors: drug therapy failure, renal failure, recurrent infection, stone formation, gross hematuria, IPSS≥20 points, Q_{max}<12 mL/s, PVR>300 ml or patient chooses the surgical treatment [2].

At the end of the last century, the term "remodeling" entered clinical practice, the essence of which is the ability of an organ to change its structure in response to a long-term pathological effect [1, 4]. L.M. Nepomnyashchikh et al. (2012) proved that the restructuring of the bladder (UB) in patients with

BPH, starting as an adaptive process, due to prolonged detrusor ischemia, leads to irreversible damage to smooth muscle cells (SMCs) and nerve cells [8].

Thus, according to the current protocols, treatment tactics in patients with BPH is based on the activity of LUTS, urodynamic parameters, and the presence of PVR. At the same time, morphological changes in the detrusor remain without attention [6].

The purpose of the study was to established the features of urinary bladder remodeling in patients with benign prostatic hyperplasia due to a long-term infravesical obstruction.

Materials and methods. The work is based on the results of examination and treatment of 1726 BPH patients in the Regional Urological Center of the Poltava Regional Clinical Hospital, named after M.V. Sklifosovsky, aged 48–89 years (M±m 69.3±6.0). Of these, 41.4 % of patients were operated in two stages, which indicates the imperfection of specialized care.

A retrospective analysis showed that, according to the clinical manifestations of UB remodeling, there are three stages: compensation, subcompensation and decompensation of UB. The stage of UB compensation can be defined as manifested LUTS (IPSS<20 points), Q_{max}>10–12 mL/s, no PVR; the stage of UB subcompensation can be defined as severe LUTS (IPSS≥20 points), Q_{max}<10–12 mL/s, PVR<200–300 ml; The stage of UB decompensation is manifested by LUTS (IPSS 30–35 points), chronic urinary retention, development of ureterohydronephrosis, recurrent urinary infection, stone formation, and renal failure.

In the next stage of the study selected 70 patients who were treated in 2019–2020, (M±m 74.9±6.8), they divided into three groups according to clinical manifestations: the first group corresponded to the UB compensation stage, the second group – to the UB subcompensation stage, the third group – the stages of UB decompensation.

The first group included 20 patients with LUTS, without PVR: IPSS–16±4.5 points, Q_{max} – 15.8±2.46 ml/s, Q_{ave} – 12.8±2.75 ml/s. The second group included 20 patients with incomplete UB emptying: IPSS – 26±3.9 points, Q_{max} – 10.79±2.53 ml/s, Q_{ave} – 4.37±1.41 ml/s, PVR – 150 14±80.83 ml. The third group included 30 patients with cystostomy: before the cystostomy: IPSS – 33.53±1.42 points, PVR – 1132.14±517.6 ml. According to the indications, the patients underwent prostatectomy, a biopsy specimen of the anterior wall of the UB was taken, which was fixed in a 10 % solution of neutral formalin at room temperature, the material was inserted in a machine for posting tissues, paraffin sections 5 μm thick were stained with hematoxylin and eosin.

Results of the study and their discussion. At the stage of UB compensation the mucous membrane is represented by a multilayered transitional urothelium, forming folds and forming pseudoepithelial outgrowths. In some areas, desquamation of the urothelium takes place, moderate dystrophic changes in individual epitheliocytes are noted, sometimes with the formation of devastation zones around the nucleus.

In the lamina propria of the mucous membrane, single focal lymphoplasmacytic infiltrations and edema are observed. In the submucosa, separate dilated lymphatic vessels, single focal lymphoplasmacytic infiltrations are visualized. The muscular layer of the UB at the stage of compensation (Fig. 1) is formed by bundles of hypertrophied smooth muscle fibers located at different angles to each other. Some myocytes show moderate hydropic dystrophy. Proliferation of urothelial and interstitial fibroblasts, increased collagen synthesis, small foci of sclerosis, and mild inflammatory infiltration are observed. Blood vessels, as a rule, are not changed, in some cases they are dilated, plethoric. In some areas, there is a moderate swelling of the interfascicular connective tissue.

A further increase in intravesical pressure, which begins to prevail over intracapillary pressure, leads to chronic multifocal detrusor ischemia.

At the stage of UB subcompensation pronounced dystrophic changes in the superficial and middle layers of the urothelium, desquamation of the superficial layers of the urothelium. The mucosa is hypertrophied, forms folds. In most cases, there is a pronounced desquamation of the urothelium and dystrophic changes in epithelial cells with the formation of devastation zones around the nucleus.

The lamina propria is edematous, with the formation of numerous lacunar clefts, which gives it a porous appearance. Blood vessels are full-blooded. In most areas, focal lymphoplasmacytic infiltration is noted. Some biopsies show fresh subepithelial hemorrhages.

In the submucosa, most of the blood vessels are plethoric. Expanded lymphatic vessels are registered. In many biopsies, the submucosa is infiltrated with lymphocytes and plasma cells, which are located in strands between hypertrophied SMCs.

The muscular layer of UB at the stage of subcompensation (Fig. 2) is formed by bundles of hypertrophied SMCs, a significant number of which are with pronounced dystrophic changes. Available areas of moderate, sometimes pronounced hydropic dystrophy. Due to the proliferation of connective tissue, muscle fibers are divided into separate bundles. Diffuse, moderately pronounced inflammatory

lymphoplasmacytic infiltration is characteristic. Blood vessels, as a rule, are dilated, plethoric. Swelling of the interfascicular connective tissue is noted. An important pathomorphological characteristic of SMCs is heterogeneity: some cells are dystrophically and necrobiotically altered, while others are only hypertrophied. Vacuolization of SMCs by sarcoplasm takes place. Significant polymorphism of the nuclei of SMCs attracts attention.

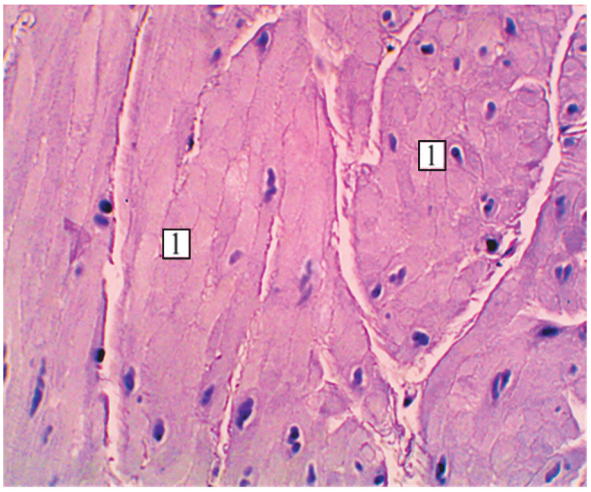

Fig. 1. The UB muscular layer at the stage of compensation. Hematoxylin and eosin staining, photographed at ×400 magnification. Bundles of hypertrophied SMCs. At the ultrastructural level: hypertrophied SMCs with some little ultrastructure changes.

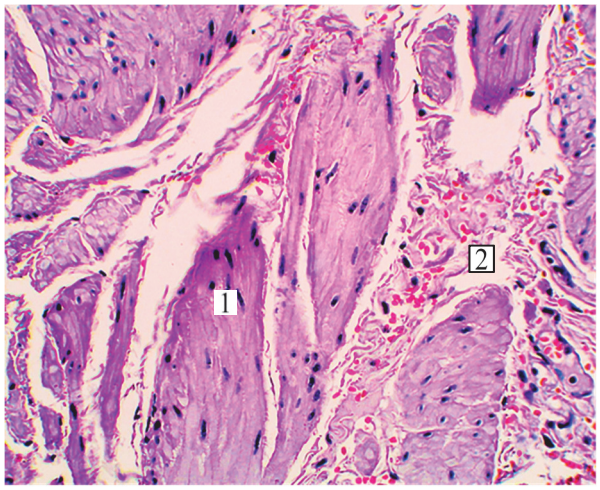

Fig. 2. The UB muscular layer at the stage of subcompensation. Hematoxylin and eosin staining, photographed at ×200 magnification. 1. SMCs with moderate hydropic dystrophy; 2. Interfascicular fibrosis.

At the ultrastructural level: hypertrophied SMCs with a slightly altered ultrastructure alternate with SMCs with a more altered ultrastructure, there are single dystrophic, so-called “dark” SMCs, the mitochondria of which are characterized by focal or total lysis of the matrix, discomplexation of organelles. There are single necrobiotically altered, so-called light SMCs, which are likely to be eliminated.

At the stage of UB decompensation urothelium was with foci of complete desquamation of all layers, dystrophic changes in epithelial cells with the formation of “devastation” zones around the nucleus.

Pronounced thickening of the mucosal lamina propria due to sclerotic changes. Numerous lacunar slits are formed, which gives the lamina propria a cellular appearance. Blood vessels are full-blooded. Diffuse lymphoplasmacytic infiltration. In most cases, lymphoid-plasmacytic follicles are observed. Most biopsies show fresh subepithelial hemorrhages.

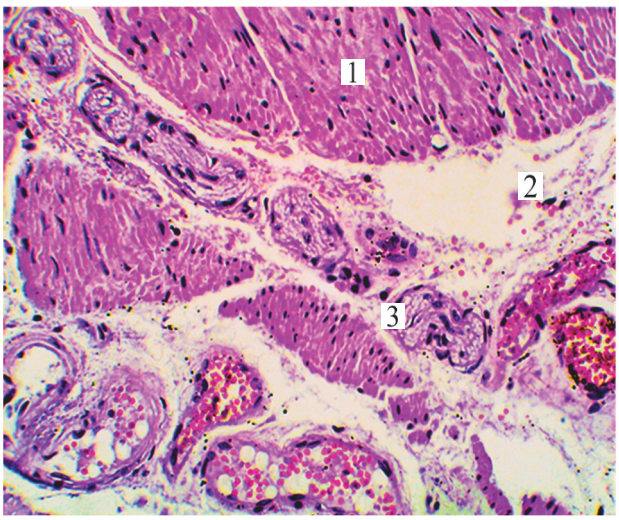

Fig. 3. The UB muscular layer at the stage of decompensation. Hematoxylin and eosin staining, photographed at ×150 magnification. 1. SMCs with pronounced hydropic dystrophy; 2. Well-developed, thick layers of connective tissue; 3. Bundles of nerve fibers with signs of dystrophy.

The submucosa is thickened due to sclerotic changes. The blood vessels are mostly plethoric. Significantly dilated lymphatic vessels are recorded. In most biopsies, the submucosa is infiltrated with lymphocytes and plasma cells, which are located in strands between hypertrophied SMCs.

In the muscular layer of the UB at the stage of decompensation (Fig. 3), there is an overgrowth of connective tissue, the layers of which divide the moderately hypertrophied, with signs of dystrophy, muscle tissue into separate bundles of different sizes. Among the connective tissue, full-blooded blood microvessels are visualized. Arterial vessels with a thickened wall and a narrowed lumen. Edematous bundles of nerve fibers are visualised.

Diffuse, pronounced inflammatory lymphoplasmacytic infiltration is noted in all layers of the UB. There are areas of pronounced hydropic dystrophy.

A characteristic sign of detrusor decompensation should be considered the formation of foci of developing sclerosis against the background of dyscirculatory disorders caused by chronic ischemia, thickening and deformation of the walls of arterial and venous microvessels. In parallel with the fibrous

compaction of the walls of arterial vessels, collagenization processes also occur in the venous segment of the vessels. The narrowing of the lumen of the vessels and a decrease in their elasticity become a prerequisite for a progressive violation of hemodynamics.

At the ultrastructural level: multiple "dark" and necrobiotically altered "light" SMCs are presented.

A long-term infravesical obstruction is accompanied by a significant decrease in the specific gravity of muscle tissue and a progressive decrease in the diameter of myocytes. Characteristically, in the detrusor decompensation stage, the specific gravity of the connective tissue was twice as high (21.78±3.39 % vs. 11.80±0.85 %; $p_2<0.05$) as compared to the detrusor subcompensation stage and three times higher (21.78±3.39 % versus 4.46±0.78 %; $p_1<0.05$) as compared to the detrusor compensation stage. The predictor of the sclerotic process is inflammatory lymphoplasmacytic infiltration in all layers of the UB.

Thus, this research confirms our previous and studies by other authors, the obstructive component is not the only pathogenetic mechanism for the development of LUTS [5, 7]. Prolonged disturbance of urine outflow and, as a result, microcirculation disorders should be considered as important factors of SMCs damage, UB sclerotic restructuring, progressive increase in residual urine, and related complications [8].

Damage to the urothelium is accompanied by a loss of the barrier function of the mucous membrane. In turn, urine permeation of all layers of UB leads to aseptic inflammation, which manifests itself in the form of lymphoplasmacytic infiltration. Chronic multifocal ischemia of the detrusor leads to progressive destructive changes of the SMCs, which is manifested by a decrease in the specific weight of muscle tissue and a decrease in the diameter of SMCs. The specific gravity of the connective tissue in the stage of decompensation of UB was almost six times higher compared to the stage of compensation and three times higher compared to the stage of subcompensation. Characteristic destructive changes in the mitochondria of SMCs indicate a violation of the ATP-synthesizing function with the development of an energy-deficient state, which negatively affects the contractile capacity of the UB. Dystrophic changes in nerve fibers lead to a decrease in neuromuscular conduction, thereby deepening the violation of the contractile ability of the UB.

The obtained data testify to the importance of the pathomorphological study of UB biopsies in order to determine further treatment tactics [2].

Conclusions

1. The study of morphological changes allows distinguishing three stages of UB remodeling in patients with BPH: compensation, subcompensation and decompensation.

2. As a result of prolonged infravesical obstruction in patients with BPH, reverse, then irreversible morphological changes in the detrusor occur with the formation of UB rigidity.

3. Substantiation of indications for surgical treatment in patients with BPH, taking into account the morphological changes in the UB, makes it possible to prevent UB decompensation and related complications.

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