DOI 10.26724/2079-8334-2021-2-76-132-135
UDC 616.65-007.61-036-06:616.62-091:616-08-048.34

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OPTIMIZATION OF TREATMENT TACTICS IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA ACCORDING TO MORPHOLOGICAL CHANGES OF THE URINARY BLADDER WALL

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60 patients with benign prostatic hyperplasia were divided into three groups according to their clinical manifestations – compensation, subcompensation and decompensation of the urinary bladder. According to the histological examination, prolonged bladder outlet obstruction leading to progressive destructive changes in smooth muscle cells, a decrease in the specific volume of muscle tissue and a decrease in the diameter of myocytes. Urothelium damage is accompanied by a loss of the barrier function, which results in sclerotic process. Substantiation of treatment tactics in patients with benign prostatic hyperplasia should be carried out taking into account the probable morphological changes in the bladder. Untimely elimination of the obstructive component leads to a loss of detrusor contractility. The therapeutic strategy for restoring detrusor contractility is to eliminate microcirculatory disorders and correct disorders of bioenergetic processes.

Key words: benign prostatic hyperplasia, decompensated urinary bladder, metabolism-corrective therapy, anticholinesterase therapy.

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ОПТИМІЗАЦІЯ ЛІКУВАЛЬНОЇ ТАКТИКИ У ХВОРИХ НА ДОБРОЯКІСНУ ГІПЕРПЛАЗІЮ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ З УРАХУВАННЯМ МОРФОЛОГІЧНИХ ЗМІН СЕЧОВОГО МІХУРА

60 хворим на доброякісну гіперплазію передміхурової залози, які за клінічними проявами були розподілені на три групи – із компенсацією, субкомпенсацією та декомпенсацією сечового міхура. За результатами гістологічного дослідження, тривала інфравезикальна обструкція призводить до прогресуючих деструктивних змін гладком'язових клітин, зниження питомої ваги м'язової тканини і зменшення діаметру міоцитів. Пошкодження уротелію супроводжується втратою бар'єрної функції, наслідком чого є розвиток склеротичного процесу. Обгрунтування лікувальної тактики у хворих на доброякісну гіперплазію передміхурової залози повинно проводитись з урахуванням ймовірних морфологічних змін сечового міхура. Несвоєчасне усунення обструктивного компоненту призводить до втрати скоротливої здатності детрузора. Терапевтична стратегія відновлення скоротливої здатності детрузора полягає в усуненні мікроциркуляторних розладів та корекції порушень біоенергетичних процесів.

Ключові слова: доброякісна гіперплазія передміхурової залози, декомпенсований сечовий міхур, метаболізм-корегуюча терапія, антихолінестеразна терапія.

This work 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.

Due to the widespread introduction of effective drugs into clinical practice during the last 30 years, the proportion of surgical interventions in benign prostatic hyperplasia (BPH) has decreased to 10–15 % [7]. In 15–32 % of all cases the surgical intervention is performed in two stages [2, 7]. The morphological studies of L.M. Nepomnyashchikh et al. (2012) proved that in case of untimely restoration of the urine passage in patients with BPH, the remodeling of the bladder, beginning as an adaptive process, leads to irreversible morphological changes in the detrusor [10]. M. Speakman et al. (2015), draw attention to the direct relationship between the amount of post void residual urine (PVR) before surgery and the frequency of lower urinary tract symptoms (LUTS) after surgery [12]. According to large-scale cohort studies, unsatisfactory results after surgery are associated with imperfect treatment standards [9].

The purpose of the study was to optimize treatment tactics in patients with benign prostatic hyperplasia according to the morphological changes of the urinary bladder.

Materials and methods. According to clinical manifestations, patients were divided into three groups. Group I included 20 patients with BPH with compensated urinary bladder, who underwent bladder biopsy during endoscopic interventions for other reasons (hematuria, urolithiasis, etc.): I-PSS – 16±4.5, Q_{max} – 15.8±2.46 ml/s, Q_{ave} – 12.8±2.75 ml/s, without residual urine. Group II included 20 patients with subcompensated urinary bladder who underwent surgical treatment of BPH: I-PSS – 26±3.9, Q_{max} – 10.79±2.53 ml/s, Q_{ave} – 4.37±1.41 ml/s, residual urine – 150.14±80.83 ml. Group III included 20 patients with decompensated urinary bladder, who underwent the second stage of surgical treatment of BPH: before cystostomy I-PSS – 33.53±1.42, residual urine – 1132.14±517.6 ml (for patients with acute urinary retention, uroflowmetry was not performed, because the effective volume of urination did not exceed 50 ml, this deprived informative value of functional study).

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The bladder wall bioptate was fixed in 10 % neutral formalin solution at room temperature, the material was processed automatically and 5 μm thick paraffin sections were stained with hematoxylin and eosin. Studies of the ultrastructure of bladder myocytes were performed by standard methods of electronic microscopy [6].

Clinical trial data was statistically processed by the method of variation statistics using Student's and Fisher`s test, determination of arithmetic mean values of indices, confidence intervals and probability values (p) was performed using the computer programs Microsoft Excel 2016. The difference was considered statistically significant at $p<0.05$.

Results of the study and their discussion. According to the results of histological examination of biopsy material in patients included in the group I of observation, the mucous membrane of the bladder had minor dystrophic changes of separate epitheliocytes. The muscle membrane is represented by hypertrophied smooth muscle cells (fig. 1). There is a moderate proliferation of urothelial and interstitial fibroblasts, small foci of sclerosis, single foci of lympho-plasmacytic infiltration.

At the ultrastructural level, there is hypertrophy of smooth muscle cells with slightly altered ultrastructure. Hypertrophy of mitochondria of leiomyocytes.

According to the results of histological examination of biopsy material in patients included in the group II of observation, the bladder mucosa is thickened, with marked dystrophic changes in the superficial and middle layers of the epithelium. Own plate and submucosal base are swollen. Significant number of smooth muscle cells are with hydropic dystrophy, heterogeneity, and nuclear polymorphism. Due to the proliferation of connective tissue, muscle fibers are divided into individual bundles (fig. 2). There is a moderate inflammatory lymphoplasmacytic infiltration in all bladder membranes.

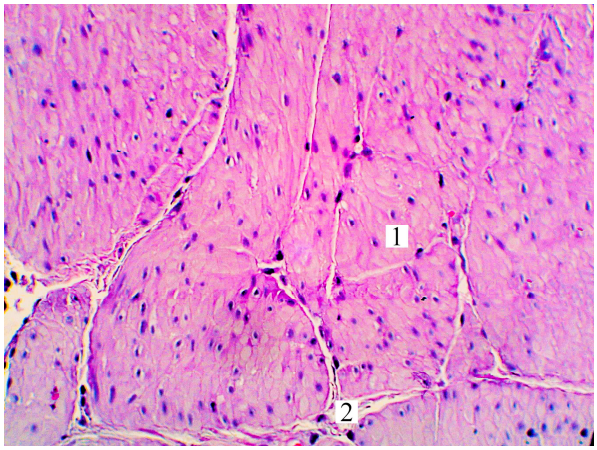

Fig. 1. The urinary bladder muscular layer. Hematoxylin and eosin staining, photographed at ×150 magnification. 1. Bundles of hypertrophied smooth muscle fibers 2. Slightly expressed layers of connective tissue

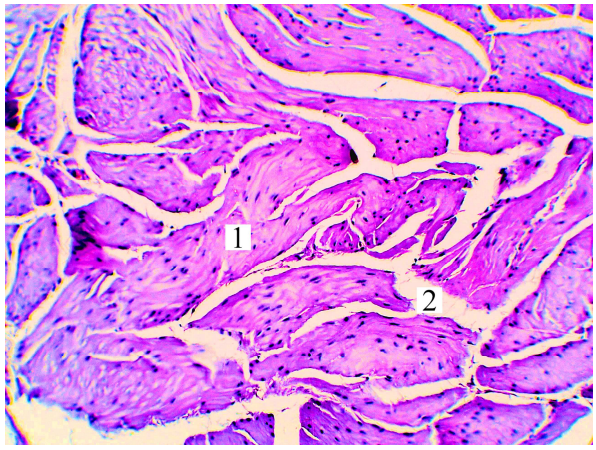

Fig. 2. The urinary bladder muscular layer. Hematoxylin and eosin staining, photographed at ×150 magnification. Smooth muscle cells with the hydropic dystrophy phenomena. Interstitial fibrosis.

At the ultrastructural level, hypertrophy of smooth muscle cells, mostly with altered ultrastructure. There are single dystrophic, so-called “dark” smooth muscle cells. Mitochondria of leiomyocytes with focal or total lysis of the matrix, destruction of the cristae and discomplexation of organelles.

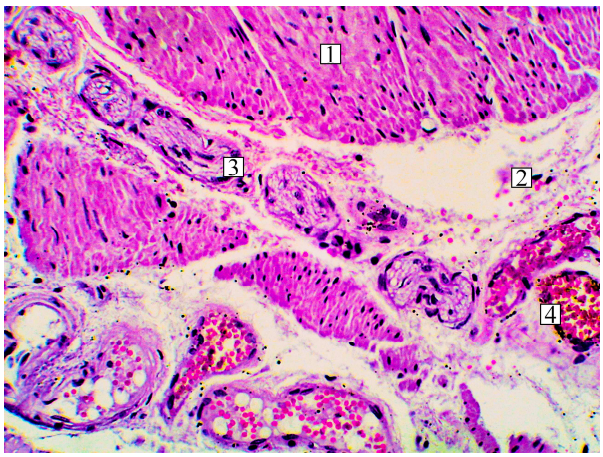

Fig. 3. The urinary bladder muscular layer. Hematoxylin and eosin staining, photographed at ×150 magnification. 1. Smooth muscle cells with severe hydropic dystrophy. 2. Massive growth of coarse fibrous connective tissue. 3. Bundles of nerve fibers with symptoms of edema and dystrophy. 4. Arterioles with plethora.

In bioptates of patients included in the group III of observation, the bladder mucosa with foci of complete desquamation and epitheliocyte dystrophy is seen. The lamina propria and submucosal base are thickened due to sclerotic changes, with numerous von Brunn's “nests”, marked lymphostasis and fresh subepithelial hemorrhages. Smooth muscle cells are with severe hydropic dystrophy. There is a progressive decrease in the diameter of myocytes. Due to the massive growth of coarse connective tissue, muscle fibers are chaotically divided into individual bundles. Most vessels are full-blooded, with a thinned wall and a narrowed lumen. There are focal, in some cases common hemorrhages. A characteristic feature of bladder decompensation is swelling of the nerve fiber bundles with pronounced signs of dystrophy (fig. 3).

At the ultrastructural level, there are multiple "dark" and necrobiotically altered "light" smooth muscle cells that need to be eliminated.

Based on the results of histological examination of biopsy material, prolonged bladder outlet obstruction in BPH due to overextension of the bladder is accompanied by microtrauma, with widespread hemorrhage. Chronic multifocal detrusor ischemia leads to progressive destructive changes in smooth muscle cells, manifested by a decrease in the proportion of muscle tissue and a decrease in myocyte diameter.

Pathognomonic destructive changes of mitochrondria of leiomyocytes indicate a violation of ATP-synthesizing function with the development of energetical deficiency and decreasing contractility of the detrusor. Damage of the urothelium is accompanied by loss of barrier function of the bladder mucosa. Thus, the impregnation of all bladder membranes with urine leads to aseptic inflammation, which manifests itself in the form of lympho-plasmacytic infiltration. The proportion of connective tissue in the stage of bladder decompensation was four times higher compared to the stage of compensation (29.46±9.06 % vs. 4.48±2.18 %; $p_1<0.05$) and three as high compared to the stage of subcompensation (29.46±9.06 % vs. 11.80±3.98 %; $p_2<0.05$) (fig. 4).

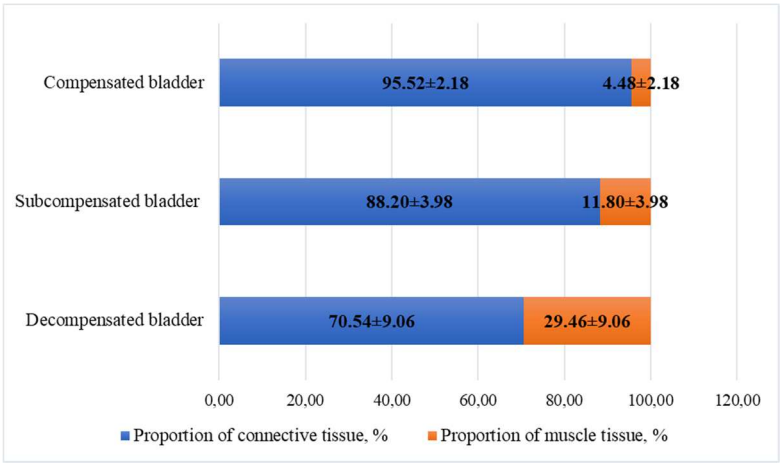

Fig. 4. The proportion ratio of the muscle and connective tissue in the observation groups.

Based on the current protocols of the European Association of Urology (EAU), the choice of treatment tactics for BPH is based on the international prostatic symptoms score (I-PSS) and urodynamic parameters.

Patients with mild LUTS (I-PSS<8 points), which do not significantly affect the quality of life, are actively monitored, with lifestyle modulation.

Indications for drug treatment of BPH are moderate (I-PSS 8–19 points) and severe (IPSS≥20 points) LUTS (EAU, 2020; AUA, 2020). Selective α-blockers (tamsulosin, silodosin, alfuzosin, terazosin) and 5-α-reductase inhibitors (finasteride, dutasteride) are considered to be the treatment of choice. Those competitively and selectively block postsynaptic α_1-adrenoreceptors, particularly α_{1A} and α_{1D}, which enter the smooth muscles of the bladder neck, prostate gland and prostatic urethra. Due to the reduction of smooth muscle tone, the symptoms of obstruction (difficulty in starting urination, weakening of urine flow) and filling (pollakiuria, nocturia, imperative urge to urinate) are reduced. The mechanism of action of 5-α-reductase inhibitors is to inhibit the activity of the enzyme responsible for the formation of dihydrotestosterone, which is considered one of the main stimulators of growth of epithelial and stromal cells of the prostate. The most marked effect is achieved with combination of therapy with selective α-blockers and 5-α-reductase inhibitors. At a volume of prostate<40 cm^3, the appointment of 5-α-reductase inhibitors is considered inappropriate and selective α-blockers are used as monotherapy [5, 7].

Since 2010, cholinolytics have been included in the therapeutic area for BPH with moderate and severe LUTS. However, antimuscarinic drugs (cholinolytics) are not recommended for patients with residual urine volume>150 cm^3 (EAU, 2010, 2017). According to the recommendations of the EAU from 2020, patients with BPH should be treated with antimuscarinic drugs taking into account the possible total anticholinergic load [3, 8]. Thus, about 600 drugs that elderly patients can take for comorbidities show anticholinergic activity. Alternatively to antimuscarinic drug, a selective β-3 adrenoceptor agonist, mirabegron, which directly affects the smooth muscles of the bladder and increases the effective volume of urination, thereby eliminating the symptoms of accumulation [4, 11].

Indications for surgical treatment of BPH are based on the activity of dysuric symptoms (IPSS≥20 points) and urodynamic parameters (Q_{max}<12 ml/sec) under conditions of ineffectiveness of drug therapy – progression of LUTS and increase of residual urine volume. In 2018, the American Urological Association (AUA) updated the recommendations, expanding the indications for surgical treatment of patients with BPH in the presence of any of the following factors: Q_{max}<10 ml/sec, PVR>300 ml, ineffectiveness of drug therapy, recurrent infection, stone formation, macrohematuria, which is not corrected by medication, renal failure or the patient choice of surgical treatment [5].

Metabolic-corrective therapy is recommended to patients with BPH with bladder decompensation to improve microcirculation and restore detrusor function. The complex of drugs, the mechanism of action of which is aimed to normalize of redox processes, stimulation of cellular respiration and ATP synthesis in the mitochondria of smooth muscle cells, includes B vitamins: octothiamine – 25 mg, riboflavin – 2.5 mg, pyriloxidine – 40 mg, cyanocobalamin – 0.25 mg, 3 times a day for 4 weeks. To improve the conductivity of nerve fibers, an anticholinesterase drug – ipidacrine – 20 mg 3 times a day for 4 weeks is recommended. The main condition for the effectiveness of surgical treatment of patients with BPH with bladder decompensation is the restoration of the contractility of the detrusor.

Conclusions

1. Substantiation of treatment tactics in patients with BPH should be carried out taking into account the probable morphological changes of the bladder.

2. Untimely removal of the obstructive component leads to progressive destructive changes in smooth muscle cells, the formation of sclerotic “skeleton”, violation of the innervation of the bladder, progressive enlargement of the PVR volume and accompanied complications.

3. In patients with BPH with bladder decompensation, the elimination of microcirculatory disorders and correction of disorders of bioenergetic processes should be considered as a therapeutic strategy to restore the contractility of the detrusor.

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Стаття надійшла 2.05.2020 р.