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MODERN APPROACH TO DRUG THERAPY FOR BENIGN PROSTATIC HYPERPLASIA

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Abstract

Benign prostatic hyperplasia (BPH) is the most common urological disease in the elderly and senile. Before the age of 40, microscopic examination reveals hyperplasia of the paraurethral glands in almost 20% of men. After 40 years, this figure reaches 40%, and by 80 years – 90% [1, 2]. The progressive development of prostatic hyperplasia underlies the occurrence of clinical symptoms of the lower urinary tract (LUTS) caused by bladder outlet obstruction, acute or chronic urinary retention, bladder stones, vesicoureteral reflux, urinary tract infection, bilateral ureterohydronephrosis and chronic renal failure. If the above manifestations are present it is necessary to resort to surgical treatment. But there is another group of men, more numerous, who have symptoms of the disease, but there are no indications for surgery. Introduced in 2001 year in Geneva in the materials of the European Urological Association, data from a survey of patients with lower urinary tract symptoms due to BPH, indicate that 58% of men deliberately reduce fluid intake in the evening; 41% avoid visiting places where there is no toilet; 31% refuse to travel long distances distances.

Key words

prostate benign hyperplasia, etiopathogenesis, types of treatment, medical therapy.

Presence of varying degrees of severity LUTS that worsen the quality of life of patients and requiring treatment determines the importance of this medical problem. It has long been clear that rational treatment tactics for BPH influence the prognosis of the disease, and surgery performed without sufficient indications may not lead to the desired result. Widespread introduction of medications into clinical practice for treatment of BPH allows you to considerHowever, the correct use of drugs that differ in their mechanism of action requires not only a lot of experience, but also knowledge pharmacology. A urologist, working with a patient, must represent the pathogenesis of urinary disorders in the elderly and the role of increased prostate in this process. A main attention attention should be paid to the correct use of the proposed treatment methods, taking into account clinical condition of the patient and his function main organs and systems. Benign prostatic hyperplasia is macroscopically a clearly defined node delimited by a capsule, located deep within the organ. Microscopically consists of epithelial parenchyma and connective tissue stroma. The epithelium in the node is often retains the ability to produce secretions, in as a result of the accumulation of which cystic cavities can form. Histological examination of the prostate gland often shows, along with the proliferation of glandular tissue, the presence of fibroadenoma (fibrous growth) and ademiomas (overgrowth of muscle fibers). In weight terms, this is accompanied by an increase in the mass of the gland from 30 to 200 grams or more. Intraoperatively, 2 or 3 are usually determined lobes (middle and two lateral), having nothing common with the atrophied prostate itself. Depending on the direction of growth of the nodes, 3 forms of the disease are distinguished: 1) intravesical form, when growth is directed into the lumen of the bladder; 2) subvesical form (most common often) – growth is directed towards the rectum; 3) retrotrigonal form (rare), when growth is directed under the vesical tringle. The obstruction is based on enlargement of the prostate gland with gradual narrowing of the lumen of the urethra (mechanical component) and increased tone smooth muscle fibers of the

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prostate and posterior urethra (dynamic component). Previously, there was an opinion that the size of the prostate gland does not determines the severity of symptoms of the disease. However, recent research has established that there is a useful correlation between these measures. It is shown that the probability moderate and severe lower urinary tract symptoms are 1.5 times higher for prostate size > 30 ml and 3.5 times higher for prostate size > 50 ml [16]. Why is the prostate gland prone to benign hyperplasia? To date, there is no explanation for the nature of this phenomenon. although a significant number of research groups are studying the cellular and molecular biology of the prostate gland foranswer to this question [5]. If we combine the works of scientists, we can state that the most widespread theory is hormonal imbalance, which is directly related to age-related changes occurring in the body of men who have stepped beyond the fifth decade years. According to this theory of estrogen-androgen imbalance, hyperplasia develops gradually from the periurethral glands and leads to enlargement of the prostate gland and hyperplasia of the glandular epithelium. Some authors speak more in favor of the importance in the development of adenoma due to estrogens, others – androgens; There are also opinions that hyperplasia begins from the cranial zone of the prostate gland itself and only then it affects the periurethral glands [5]. The role of the biomicroelement is very interesting zinc in the possible development of prostatic hyperplasia due to participation in the regulation testosterone metabolism. The role is being actively explored prostate specific antigen. The bulk of this antigen is synthesized in the cells of the glandular epithelium of the prostate and further excreted through ducts into the prostatic part of the urethra, mixing with components of seminal fluid during ejaculation or secretion. Currently, differences in the structure have been discovered RNA transcripts and prostate specific antigen in normal and pathologically altered prostate tissue. The probable biological significance of prostate specific antigen production in the prostate may be as follows. Firstly, the high proteolytic activity of prostate juice and mixed seminal fluid, mainly caused by this antigen, ensures after ejaculation the breakdown of the high-molecular protein of seminal fluid - seminogelin. This reduces the viscosity of seminal fluid and possibly increases motility sperm, although the latter has not been proven. Secondly, proteolysis of fibronectin, which is part of the seminal fluid, occurs, and, possibly, which is an inhibitor of cell growth factors prostate. Thirdly, it is known that insulin-like growth factors (IGFs) are formed in prostate stromal cells, which act paracrine to neighboring epithelial cells, having appropriate receptors, and stimulate their reproduction. Mitogenic effect IGFs are limited by special proteins that bind IPFR. Found in human seminal fluid several such proteins. These proteins, being in stromal cells probably reduce the mitogenic activity of IGF towards prostate epithelial cells. Active prostate specific antigen in prostate tissue catalyzes the proteolysis of the above special proteins and thus enhances proliferation these cells. Therefore, prostatic a specific antigen, indirectly activating IGF, can regulate and accelerate proliferation of epithelial cells as in healthy and pathologically altered prostate gland. The question of the relationship in normal and pathological conditions between prostate specific antigen, androgens, peptide growth factors, as well as androgen and growth factor receptors. It has now been established that in prostate stromal cells from testosterone Dihydrotestosterone (DTS) is synthesized which, enhancing transcription in the same cells, induces in them the synthesis of various peptides growth factors (GFR), their receptors and 5-alpha reductase. The resulting PFR and DTS act autocrine on the stromal cell, as well as paracrine reach the epithelial cells of the prostate, enhancing the synthesis of RNA, proteins, including PFR and prostate specific antigen. All this together leads to accelerated proliferation of epithelial cells. With age in men, the production of DTS in the prostate gland increases, which is still not received a convincing xplanation. Increased DTS content in the prostate, caused by age-related or other factors, may be one from benign or malignant hyperplastic processes.

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In in recent decades, thanks to numerous studies in the theory of the pathogenesis of BPH significant changes have occurred. Revealed the role of the hypothalamic-pituitary-gonadal system in control of growth, development and function of the prostate gland. One of the main provisions of the theory of BPH pathogenesis is the role of the enzyme 5- -reductase and dihydrotestosterone (DHT) [15, 16]. In BPH, there is an increase in 5- -reductase activity and a hormonal imbalance associated with DHT. Violation of the enzymatic balance leads to loss of control over the course of intracellular metabolic processes and contributes to the development BPH, which manifests itself as an overgrowth hyperplastic prostate tissue (mechanical factor); increased activity and tone 1- adrenergic receptors of the prostate gland, bladder neck and prostate urethra, leading to hypertonicity (spasm) of their smooth muscle structures (dynamic component); metabolic disorders in prostate tissue, leading to circulatory disorders of these organs and aseptic inflammation. Recent work has emphasized the importance of the stroma and stromal-epithelial relationships in inducing hyperplastic growth in BPH. The development, differentiation, proliferation and maintenance of prostatic cell viability are regulated by subtle interactions of stimulating and inhibitory growth factors. Research by Laurent O.B. and Vishnevsky E.L. was the role of wall circulatory disturbances is shown bladder, detrusor ischemia and wasting its energy capabilities in pathogenesis urinary disorders. The degree of severity of morphological changes in the bladder wall (severity of sclerotic processes, atrophy of detrusor muscle fibers) also plays an important role in the genesis of BPH. Both types of α-adrenergic receptors are found in the bladder, but the increase in the tone of the smooth muscles of the neck, urethra, and prostate is associated with α1-adrenergic receptors, which have a high density here. Subtypes of α1-adrenergic receptors (A, B, D) in recently found in the lower sections urinary tract and prostate. In healthy people in the prostate 69.3% of α1-adrenergic receptors belong to subtype A, whereas with BPH there are many of them more – up to 85%. In BPH, there is increased activity of α1-adrenergic receptors, leading to a spastic state of the base of the bladder, posterior urethra and smooth muscle elements of the prostate, therefore there is the possibility of a significant reduction in urethral resistance in patients with BPH when the interaction of the mediator of the sympathetic nervous system with α1-adrenergic receptors is disrupted. Clinical symptoms and diagnosis of BPH With BPH, urination disturbances are noted: increased frequency, initially predominantly at night, sluggish urine stream, feeling of incompleteness bladder emptying, intermittency streams of urine. Under the influence of various factors Acute urinary retention may occur. Clinical manifestations of urinary disorders due to BPH are divided into two groups. Obstructive symptoms are caused by the proliferation of hyperplastic prostate tissue, irritative symptoms are caused by an increase in the activity of 1- adrenergic receptors of the prostate gland, cervix bladder and prostatic urethra, disruption of metabolic processes in prostate tissue, leading to circulatory disorders of these organs and aseptic inflammation.

Surgery. The only radical method of removing hyperplastic prostate tissue (adenoma) is surgical. However, even the most “golden” standard” – transurethral adenomectomy (TURP) is not without complications. The most formidable one of them is bleeding. In 8% of cases of TUR there is a need for a blood transfusion. This the value can increase up to 20% with volumes hyperplastic prostate more than 100 cm3 . Indications for surgical treatment are recurrent acute urinary retention; formation of bladder stones; progression of chronic renal failure due to bladder outlet obstruction; recurrent purulent-inflammatory processes of the urinary tract; recurring gross hematuria, as well as lack of effect from drug treatment. Drug therapy is indicated for patients in which irritative symptoms predominate. The most widely used inhibitors are 5- -reductase inhibitors, alpha-1 adrenergic blockers and herbal preparations. It is unlawful to give preference to any of the them,

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without taking into account the clinical manifestations of the disease, the volume of the hyperplastic prostate, the severity and characteristics of urination disorders and disorders of the functional state of the bladder, the possibility of the occurrence and nature of adverse reactions. Modern drugs can significantly reduce symptoms diseases and improve urination performance. This, first of all, applies to drugs with proven effectiveness and safety. When choosing a treatment strategy, it is necessary take into account the patient's risk factors progression of BPH. Progression defined as the worsening of a disease over time. The degree of progression is determined by the degree of change in the main symptoms illness and lack of effect from the treatment treatment. Study using a special protocol MTOPS (Medical Therapy of Prostatic Symptoms), which included more than 3000 patients with BPH, observed from 4 to 6 years, showed that, 17% of patients with BPH have signs of disease progression, which is manifested by an increase in IPSS > 4, the appearance of acute delay urination, urinary incontinence, kidney failure, or recurrent infection urinary tract. It has been established that the most significant criteria for the progress of prostate hyperplasia are the level of prostate specific antigen (PSA) in the blood serum of more than 1.4 ng/ml; volume of hyperplastic prostate exceeding 40 cm3 ; score indicator symptoms on the IPSS scale more than 7 and a decrease in the maximum volumetric flow rate of urine less than 10 ml/s. In the absence of adequate treatment, each of these criteria increases the risk of acute urinary retention or surgical intervened. May also be important as prognostic factors belong to the direction of growth of the hyperplastic prostate, its morphological structure, blood circulation of the prostate gland and detrusor, functional state and reserve capabilities of the bladder. In addition, age patient and the presence of concomitant diseases play a significant role in the choice of treatment tactics. In the fourth category of patients, there is a significant enlargement of the prostate gland in size is combined with the severity of symptoms lower urinary tract, but these indicators are not so great as to be recommended to patients surgical treatment. Reduction of smooth muscles of the prostate interstitium and adenomatous tissue can account for 40% of the size of the obstruction Out flow of urine. This group of patients is the most severe. They are shown a combined therapy – 5- -reductase blocker in combination with an alpha-blocker. Such therapy due to dual mechanism of action reduces volume prostate gland (the result of the action of 5- -reductase inhibitors), increases the maximum flow rate of urine and significantly reduces severity of symptoms (result of action α-blockers). The effectiveness of such treatment – 95.5%. It is known that BPH leads to an increase in activity of the sympathetic nervous system, which causes an increase in smooth muscle tone structures of the base of the bladder and prostate gland. Adrenergic blockers cause relaxation of the smooth muscles of the listed structures by blocking α1-adrenergic receptors, as a result, the severity of the dynamic component of lower urinary tract symptoms decreases. Combination therapy with finasteride, which inhibits cell proliferation on hormonal level and α-blockers affecting the smooth muscle component of the stroma prostate, allows you to influence all components of obstruction in BPH, which is significant improves therapy results. Therefore, finasteride with alpha-blockers is ideal combination with a combination of acute disorders urination with large prostate sizes in patients with BPH. When this combination is used, the positive qualities of each drug appear, complementary each other. Thus, β-blockers provide a rapid treatment effect, while finasteride provides a 25% reduction in the size of the prostate gland by the end of the course of treatment. Frequency of invasive interventions during treatment with finasteride and in combination therapy significantly reduced by 64 and 67% compared to placebo [13]. Thus, the given data says about the effectiveness of drug therapy, its ability not only to alleviate the suffering of patients, but also in some cases to avoid surgery or create better conditions for surgical treatment. Of course, due to different options clinical course of the disease, the predominance of irritative or

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obstructive symptoms it is necessary to take a differentiated approach to the treatment of BPH, choosing monotherapy with alpha-blockers, 5-α-reductase inhibitors or combination therapy. Necessary evaluate the effect of treatment using clinical and instrumental urodynamics methods. Possibilities of pharmacological correction the act of urination is quite large. Search for optimal combinations of drugs and technology application will certainly produce results.

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