LECTURES

CURRENT CONCEPTS OF PEYRONIE'S DISEASE (CLINICAL LECTURE)

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ABSTRACT

The article is presented in the format of a lecture. Peyronie's disease (induratio penis plastica) is a progressive fibrotic disorder of the penile tunica albuginea that results in fibrotic penile plaques and can cause penile deformity. The issues of etiology, pathogenesis, clinical picture and diagnosis of Peyronie's disease (PD) are reviewed in the lecture from the modern points of view. PD is frequently associated with penile pain, erectile dysfunction, and a secondary anxiety-depressive state. Despite the existence of this problem for several centuries, no unified concept of the Peyronie's disease pathogenesis can be found in literature. A growing amount of research has shown that PD is a chronical disorder of local wound healing process within the tunica albuginea and the Smith's space. Over the past 40 years, multiple lines of evidence have pointed to a genetic factor that predisposes some men to the development of Peyronie's disease. Treating men with PD remains a challenging problem for clinicians working in urology. Given the high prevalence of PD and its significant impact on affected men, its better understanding is essential. Treatment methods for PD are varied and include oral, local, intralesional and traction therapy, and surgical treatment. Current clinical care standards for PD are aimed at the symptom suppression, as there are currently no treatment for PD that can eliminate its causes or progression. Clostridium histolyticum collagenase has shown its effectiveness in treating PD, but its efficacy and safety remain controversial. Surgery remains the most effective method for PD treatment and is considered to be "gold standard". The choice of the surgical technique depends on the length of the penis, degree of deformity, erectile function, patients' expectations and surgeon's preferences. Various surgical techniques and grafting materials (autologous and non-autologous) can be used for the coverage of the tunica albuginea defect after partial plaque excision or incision.

Key words: *fibroplastic penile induration, Peyronie's disease, curvature of the penis, erectile dysfunction, substitutive corporoplasty, buccal graft*

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АКТУАЛЬНЫЕ ПРЕДСТАВЛЕНИЯ О БОЛЕЗНИ ПЕЙРОНИ (КЛИНИЧЕСКАЯ ЛЕКЦИЯ)

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РЕЗЮМЕ

Статья представлена в формате лекционного материала. Болезнь Пейрони (фибропластическая индурация полового члена) представляет собой прогрессирующее фиброзное заболевание белочной оболочки полового члена, которое приводит к образованию фиброзных бляшек и может приводить к пенильной деформации. В лекции с современных позиций рассмотрены вопросы этиологии, патогенеза, клиники и диагностики болезни Пейрони (БП). БП часто сочетается с болью в половом члене, эректильной дисфункцией и вторичным тревожно-депрессивным состоянием. Несмотря на то, что эта проблема сохраняется не одно столетие, на сегодняшний день в литературе нет единой концепции патогенеза. Растущий объём исследований показывает, что БП представляет собой хроническое нарушение локального процесса заживления ран в белочной оболочке и пространстве Смита. За последние 40 лет многочисленные доказательства указывают на генетический фактор, предрасполагающий некоторых мужчин к развитию БП. Лечение мужчин с БП остаётся сложной проблемой, стоящей перед клиницистами, работающими в области урологии. Методы лечения БП разнообразны и включают пероральную, местную, внутриочаговую и тракционную терапию, оперативное лечение. Действующие стандарты клинической помощи при БП направлены на устранение симптомов, поскольку в настоящее время не разработаны методы лечения, направленные на ликвидацию причин, вызывающих её и способствующих прогрессированию заболевания. Коллагеназа Clostridium histolyticum показала свою эффективность в лечении БП, но её эффективность и безопасность остаются спорными. Хирургия остаётся наиболее эффективным методом лечения БП и считается золотым стандартом. Выбор хирургической техники зависит от длины полового члена, степени деформации, эректильной функции, ожиданий пациентов и предпочтений хирурга. Для закрытия дефекта белочной оболочки после частичного иссечения или разреза бляшки можно использовать различные хирургические методики и трансплантационные материалы (аутологичные и неаутологичные).

Ключевые слова: *фибропластическая индурация полового члена, болезнь Пейрони, искривление полового члена, эректильная дисфункция, заместительная корпоропластика, буккальный трансплантат*

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The strategy of preserving men's health in the Russian Federation is an important and integral part of the health of the nation. In the conditions of modern life, more and more attention in the scientific literature is paid to diseases that lead to a significant decrease in the quality of life of patients and their social maladjustment. This clinical lecture presents generally accepted, effective methods of diagnosis and treatment of an urgent problem of modern uroandrology that causes pathological dysfunction of the penis; it also describes new strategies used in the treatment of this disease, which have successfully proven themselves in clinical practice. Peyronie's disease (PD), as well as erectile dysfunction and premature ejaculation, are attributed to violations of male sexual function. This rather mysterious, although not rare disease was named after the French surgeon, physician in ordinary to Louis XV Francois Gigot de La Peyronie (François Gigot de La Peyronie, 1678–1747) [1]. It should be recognized that much attention has been paid to the problem of fibroplastic penile induration for several centuries, but it is far from being resolved, leaving many unresolved issues related not only to the disruption of the appearance of the erect penis, but also to changes affecting various spheres of a man's life (intimate, psychosocial, functional). The prevalence of erectile dysfunction among PD patients ranges from 40 to 60 % [2]. Another aspect that should be paid attention to is sexual distress, which negatively affects the quality of life not only of the patients themselves, but also of their partners.

In his book on the violation of ejaculation (1743), one of the founders of the French Academy of Surgery, F.G. de La Peyronie wrote about the "lumps" of cavernous bodies in the form of "rosaries", leading to curvature of the penis. However, several centuries before the publication of de La Peyronie pathological curvature of the penis has been studied and described by many surgeons and anatomists: Theodoricus Borgognoni (1205–1298), Guilielmus of Saliceto (1210–1276), Gabriele Falloppio (1523–1562), Andreas Vesalius (1514–1564), Giulio Cesare Aranzi (1530–1589), Claas Pieterzoon Tulp (1593–1674), and Anton Frederik Ruysch (1638–1731). The latter are supposed to have left the first "posthumous" illustration of this pathological condition on a copper engraving (1691). Of all the listed predecessors, F.G. de La Peyronie, only Guillelmus of Saliceto and Falloppio were involved in the treatment of the disease.

DEFINITION AND TERMINOLOGY

Fibroplastic penile induration (induratio penis plastica), or Peyronie's disease, is understood to be a relatively common, acquired, progressive, benign connective tissue disease associated with the uncontrolled formation of fibrous/calcified inelastic plaques on the tunica albuginea and adjacent cavernous tissue of the penis, accompanied by deformation (curvature, shortening) penis in an erect or semi-erect state, with a painful erection, followed by the development of erectile dysfunction (ED) and a decrease in the quality of life of a man. In most cases, PD develops as a result of repeated, often unrecognized and minor micro-injuries of the penis during sexual intercourse. The progression of the condition can occur over several years. In some cases, it can occur as a spontaneously self-healing condition (13 %) [3]. Clinically, PD is manifested by the presence of a palpable plaque, curvature or penis shortening / narrowing, the occurrence of pain discomfort during erection or sexual intercourse, ED, various psychological disorders. Currently, the pathological condition is considered to be a local manifestation of systemic collagenosis.

EPIDEMIOLOGY

To date, there are no cohort data clearly describing the incidence and/or prevalence of PD in the general population, and epidemiological data on the disease in different countries are limited and ambiguous. Different levels of epidemiological studies were conducted in the USA, Germany, Italy, Australia, Turkey, and Japan, while in Eastern Europe, including Russia, epidemiological data on PD is very small. The prevalence rate of PD, according to the first study conducted in the USA in 1991, is 0.38 % (388.6 per 100,000 population), and the average age of patients who sought medical help reached 53 years with a range from 19 to 83 years [4, 5]. The results of the first large-scale cross-sectional study, published in 2001 in the British Urological Journal, allowed us to establish the prevalence of fibroplastic induration of penis in a sample (n = 8000) of surveyed German men aged 30–80 years at the level of 3.2 %, which is much higher than indicated in previous studies [6]. Generalized prevalence of PD in the general adult male population, according to M.G. Manka et al. (2021), ranged from 3 % to 9 %, and in certain groups of the adult population – from 0.39 % to 22.5 % [7]. Modern scientific data suggest that the actual number of patients reaches higher values, and PD itself is usually attributed to an undiagnosed pathology. It was found that in the US population it ranges from 0.5 % to 13 % [8], Italy – 7.1 % [9], Germany – 2.7 % [10], Japan – 0.6 % [11], Turkey – 5.3 % [12]. According to P.A. Shcheplev et al., the prevalence of PD in the Russian Federation reaches 3-8 % in terms of urological care and up to 25 % according to the results of pathoanatomical autopsies [13]. PD is registered everywhere, but the number of cases in the population varies depending on the continent, race, and age. The disease is more common in the population of men of the older age group – usually 50–60 years old. At the same time, personal experience shows that PD occurs at an earlier age: thus, the prevalence in adulthood is about 8 %, is characterized by an acute onset and is accompanied by a lower incidence of ED [14, 15]. The prevalence in the four age groups of adult men (30–39, 40–49, 50–59 and 60–69 years old) was 1.5 %, 3 %, 3 % and 4 %, respectively, and its peak was in men over 70 years old (6,5 %) [14, 15].

RISK FACTORS

The leading risk factors for the development of PD are diabetes mellitus, lipid metabolism disorders, arterial hypertension, ED, smoking, alcohol abuse, androgen deficiency and operations on organs of the genitourinary system (radical prostatectomy, transurethral resection), ischemic cardiomyopathy, autoimmune diseases [16]. PD is detected in 8 % of cases in patients with type 2 diabetes mellitus (DM) and in 20 % of patients with hyperglycemia and ED. The risk of developing PD increases by 16 % among Caucasian men after radical prostatectomy [17]. When screening for prostate cancer in a cohort of 534 men, 6 % of patients reported the presence of penis curvature, and 8.9 % had a Peyronie plaque on physical examination [18]. Smoking is closely related to PD, and a connection has been established between the incidence of the disease and the number of cigarettes consumed per day [19], the early onset of tobacco smoking and its duration [20]. A fairly strong argument in favor of a causal relationship indicating a genetic predisposition of the disease is the identification of the features of the prevalence of PD among different ethnic groups. PD is more common in men of the Caucasian race than in representatives of other nationalities, which suggests the presence of a «founder» mutation effect (loss of genetic variability). Dupuytren contracture is common in patients with PD (8.3–39 %), and PD is detected in 4–26 % of patients with Dupuytren contracture. At the same time, genetic changes in men with both PD and Dupuytren contracture are independent factors supporting the risk of developing cancer of the genitourinary system and gastrointestinal tract compared with men of the same age only with ED and the control group [21, 22]. These data suggest that men with PD should be closely monitored not only after diagnosis, but also after treatment of the disease [22]. Men with PD had an increased risk of developing stomach cancer (hazard ratio (HR) – 1.43; 95% confidence interval (95% CI): 1.06–1.14), testicular cancer (HR = 1.39; 95% CI: 1.05–1.84) and melanoma (HR = 1.19; 95% CI: 1.02–1.38) due to genetic abnormalities contributing to the development of PD: duplications of chromosomes 7 and 8, Y-chromosome deletions and structural changes such as reciprocal translocations 46XY,t(11;12)(q11,p11), 46XY,t(1;5)(q25;q11) and others [23]. However, the specific genetic factors that predispose PD patients to develop not only a number of hereditary diseases, but also malignant neoplasms, have not been definitively established.

Non-gonococcal urethritis, inflammatory diseases of the genitourinary system in a partner, as well as fibromatous lesions of the genitals are among the modifiable risk factors that can be influenced. The study of the role of hormonal shifts as a factor contributing to the development of PD did not lead to convincing evidence, even though low testosterone levels were found in 74.4 % of patients with PD [23]. In 2022, Japanese scientists have identified a correlation between AB0 blood groups and the development of PD: Japanese men with blood type 0 had a high risk of developing PD, while men with group B had a low risk [24].

ETIOLOGY AND PATHOGENESIS

The etiology of PD is multifactorial, and the mechanisms of disease development continue to be insufficiently studied. In most cases, sexual intercourse and vaginal intromission are considered to be provoking PD events with semi-erect penis. Currently, many researchers share the opinion that there are several theories of the pathogenesis of PD: microtraumatic (posttraumatic), endocrine, genetic, connective tissue pathology, chemical and vegetative. From the numerous proposed theories, micro/macrotrauma of the tunica albuginea and damage to the microcirculatory bed of the penis in genetically predisposed men are postulated. Penile injury can be caused by acute and chronic conditions such as accidents or surgical interventions, but it can also be associated with repeated microtrauma during sexual intercourse. Despite the fact that all men are more or less exposed to penis microtrauma during sex, only very few develop PD. An interesting fact indicating the multifactorial nature of the disease is the observation of PD in sexually inactive men who have never had sexual intercourse with penetration [25]. The anatomical location of the vessels crossing the tunica albuginea of the penis is unique. Repeated traumatic damage to the microvessels of the tunica albuginea causes local aseptic inflammation with destruction of elastic fibers and deposition of fibrin. Fibrin deposition is one of the initial consequences of damage to microvessels in the penis. A prolonged inflammatory response leads to the remodeling of connective tissue into dense fibrous plaques, and the formation of the latter causes curvature, which, if severe, can interfere with the copulatory function of a man. The arteries are protected by a cuff made of loose areolar tissue, while the veins are in direct contact with the fibrous membrane. If the fibers of the tunica albuginea of the penis are damaged by micro/macrotrauma with extravasation, then edema and cellular infiltration compress neighboring venous vessels and form a «trap» for an inflammatory reaction. The production of intercellular matrix and collagen fibers is further stimulated by the secretion of leukocytes and macrophages, as well as the release of cytokines. Since inflammation is limited, cytokines cannot disperse and break down, stimulating the production of even more cytokines, which consistently provoke the production of intercellular matrix and collagen [26]. All of the above allows us to consider PD as an abnormal wound healing process in response to local aseptic inflammation (a genetically aberrant healing process), which is limited by layers of the tunica albuginea (Smith space, Buck's fascia). The triggered mechanism with the accumulation of inflammatory cells and the formation of reactive oxygen intermediates, activation of fibroblasts and myofibroblasts, excessive collagen production between the layers of the tunica albuginea leads to a violation of function and structural balance – active growth of collagen fibers, fragmentation of elastic fibers, accompanied by histological changes of an inflammatory nature, which ultimately leads to the re-accumulation of collagen and the formation of a Peyronie fi-

brous plaque. Oxidative stress in the form of free radicals such as superoxide, peroxynitrite and the resulting peroxides leads to lipid peroxidation and further tissue damage [26]. Peroxynitrite, a profibrous compound, has a cytotoxic effect through various mechanisms of lipid peroxidation, DNA fragmentation, damage and nitration of proteins directly on the smooth muscle tissue of the penis cavernous part [26]. Fibrin is a powerful chemoattractant, a chemical that directs the migration of cells sensitive to them. The final process of fibrin replacement in the tunica albuginea of the penis lasts from 12 to 18 months, the curvature of the penis is completely formed, passing through seven successive stages: from injury to the tunica albuginea, loss of fibrinogen, increased local inflammation, growth of myofibroblasts with abnormal location, formation of collagen and deposits, pathological deposition of fibrin and to the formation of plaque [26]. The regulation of collagen synthesis by many endogenous and exogenous peptides plays a key role in the pathogenesis of PD. Tumor growth factor β (TGF-β) in recent studies has interested scientists as a cytokine that affects the deposition of intracellular matrix and induces fibrosis in the tunica albuginea of the penis [27]. TGF-β is also a cause of various chronic fibrotic conditions. Overexpression of TGF-β is also observed in plaques in PD. Some studies have shown that vascular injury leads to the formation of osteoids through osteoblast-like cells originating from the vascular lumen [28]. More recent reports have focused on the activation of certain genes, namely factor 1, specific to osteoblasts, which may be responsible for plaque calcification [29]. At the beginning of the pathological process, inflammation and swelling irritate the nerve endings, causing pain. As the inflammatory reaction subsides, nerve fibers may become ischemic and necrotic. In the chronic phase of the formation of the Peyronie plaque, fibrosis accelerates and prevents the development of an erection, which often leads to ED. Arterial insufficiency caused by direct obstruction by fibrous plaques of nearby cavernous arteries is believed to impede blood flow [30]. In the chronic phase of PD, when the plaque is stable, it often penetrates into the architecture of the penis smooth muscles, which leads to venoocclusive dysfunction.

Numerous studies indicate that there is a genetic contribution that predisposes men to the development of PD: changes in gene expression in plaques; karyotypic abnormality; single nucleotide polymorphism; frequent detection of class II antigens of the HLA – HLA-DR3 and HLA-DQW2 systems [26, 31]. At the same time, despite the progress made in understanding the role of genetic factors in PD, the data remain extremely contradictory, and the genes responsible for the development of the disease have not been identified.

Clinical and experimental studies indicate an important role in the formation of pathological penis deviation the pathology of connective tissue: Dupuytren contracture, Ledderhose disease, scapulohumeral periarthritis, scleroderma, dermomyositis and sclerosis of the auricles, as well as hormonal imbalance (the participation of androgens in collagen metabolism and wound healing) [32].

PHASES OF THE PROGRESSION. CLINICAL MANIFESTATIONS. CLASSIFICATION

Considering PD from the perspective of the dynamic progression of the disease, it is extremely important to distinguish between two phases accompanied by different symptoms, which further determine the choice of treatment method (conservative or surgical). According to international recommendations [33], the first (active) or acute inflammatory phase is distinguished, which is characterized by a variety of dynamically changing clinical signs and symptoms. The duration of the active phase ranges from 12 to 18 months. The first phase is accompanied by penile pain syndrome in the non-erect and erect state; at this stage, soft nodules /plaques form and begin to palpate; sometimes it can simultaneously be accompanied by the development of penis curvature, in some cases, signs of ED appear. A distinctive feature of the first phase is the presence of an inflammatory infiltrate in the tunica albuginea of the penis. Most often, the first manifestation of PD is penis deformation (52–94 %), followed by pain, which is noted in the early stages of the disease by 20 to 70 % of patients. The second phase – fibrotic (chronic, stable) – is characterized by the formation of hard / hard palpable plaques, which can later calcify, bringing the pathological process closer to the stabilization of the disease. This phase is characterized by the disappearance of pain during erection and increased penis curvature for three months. In some cases, stabilization of the process may begin earlier – at the 5th or 7th month from the onset of the disease. Over time, penis curvature increases in 21–48 % of patients, and in 36–67 % of patients it remains stable [33]. Spontaneous improvement of the disease is rare (3–13 %), in most cases there is progression (21–48 %) and stabilization of the disease (36–67 %) [34]. Pain syndrome is usually present at an early stage and in 90 % of cases resolves within the first 12 months [34]. In 39 % of patients, palpable plaques appear first, most often located on the penis dorsal surface [34]. At a later date, there is a lack of tumescence of distal to the penis affected area. In addition to pain and painful erections, penis curvature, erectile dysfunction, the presence of palpable lumps in the penis, the most terrible thing for a man is the inability to participate in sexual relations with penetration. In addition to the physical and sexual symptoms of PD, many men experience emotional and psychological disorders.

According to the coding criteria of the International Classification of Diseases of the tenth revision, fibroplastic penile induration and fibrosis of the cavernous bodies were assigned to one nosological group – plastic penile induration. The stage classification of V.E. Maso (1984) subdivides pathology into four stages. At the first stage, the Peyronie plaque is not palpated or visualized, the only clinical manifestation is pain during erection. The second stage of PD is characterized by the appearance of a palpable fibrous-elastic formation on the tuni-

ca albuginea of the penis. At the third stage of PD, dense fibrous-elastic fibers are detected during histological examination. The appearance of calcifications in the Peyronie plaque indicates the fourth stage of the process [35], which is divided into two periods – painful and functional. The pain period is characterized by the presence of only pain both during arousal and without it, and the functional period is characterized by penis curvature, which prevents sexual intercourse, ED. Researchers F. Iacono et al. (1993) proposed a classification based on the duration of the progression (up to 6 months; from 7 to 12 months; more than a year) of the disease [36]. The classification of A. Kelami (1983) has become widespread, which implies the allocation of three degrees (light, medium, severe): thus, the angle of penis curvature up to 30° and the size of the Peyronie plaque 2 cm is attributed to a mild degree; the angle of penis curvature from 30 to 60° and the size of the plaque from 2 to 4 cm is medium; the angle of penis curvature is greater than 60 ° and the size of the plaque more than 4 cm is severe. [37]. The shape of an erect penis depends on the size of Peyronie's plaques. The classification of PD proposed by I.I. Gorpinchenko and Yu.N. Gurzhenko is the most complete, focused on various aspects of the disease (features of the progression, clinical manifestations, plaque localization, direction of curvature, complications, concomitant diseases), balanced for the choice of surgical tactics [38]. According to the progression, the authors differentiate PD into slowly and rapidly progressing forms. Among the clinical manifestations are: pain (0 – absence; 1 – minor pain during erection; 2 – significant pain, hindering sexual activity; 3 – pain during erection and without erection); curvature (0 – absence; 1 – up to 30° without restriction of sexual activity; 2 – up to 60° with restrictions on sexual activity; 3 – more than 60° with the impossibility of sexual activity); lump (0 – absent; 1 – up to 1 cm in diameter; 2 – 1–3 cm in diameter; 3 – more than 3 cm in diameter). According to the localization of Peyronie plaques, there are: 1 – at the root of the penis; 2 – in the area of the stem of the penis; 3 – at the head of the penis; in the direction of curvature – dorsal, lateral, dorsolateral, dorsolateral right; by the presence of complications – with or without preservation of erectile function; by the presence of concomitant diseases – with or without concomitant diseases.

DIAGNOSTICS

The best diagnostic indicators of the disease are still a detailed medical history and physical examination. The purpose of the clinical examination of patients is to establish the correct diagnosis necessary for the timely initiation of both conservative and surgical treatment, which is the main method at a late stage (stabilization) of the disease. In most cases, the patient actively complains about the curvature and penis shortening, the pain during erection, the formation of lumps/nodules in the penis, as well as the impossibility of introjection, in some cases – the absence of erections and the appearance of psychoemotional disorders. The above complaints are not always the reason for immediate medical attention. The survey allows you to determine not only the trigger that provoked the appearance of complaints, but also the timing of their appearance and disappearance, especially pain syndrome, the first signs of ED, penis curvature and deformation. It is advisable to obtain information about the family history of the disease, cases of PD or other fibrous processes (Dupuytren contracture and Ledderhose disease in close relatives, etc.).

Psychometric analysis makes it possible to evaluate sexual function using the International Index of Erectile Function. An important question should be asked: "Would you be able to have full sexual intercourse if you did not have a penile deformity?". A tool has been developed to assess the progression and severity of symptoms of the disease, known as the Peyronie's Disease Questionnaire, containing 15 questions [39]. In the presence of depression, it is recommended to use the Beck Depressive Inventory scale [39]. The development of ED and psychological changes has a significant influence on the choice of treatment.

The purpose of the physical examination is not only to detect penile deforming changes but also to identify contractures, sclerodermic changes. Vacuum erectors are used to determine the severity of the curvature. The following types of penis deformation are distinguished: dorsal (68 %) – upward curvature; ventral (1 %) – downward curvature; lateral (15 %) – sideways curvature; dorsolateral – upward and sideways curvature; ventrolateral – downward and sideways curvature; «hinge» type deformation – local curvature narrowing and instability of the part of the penis located behind the narrowing; narrowing of the organ along the circumference is an "hourglass" type deformation [39]. Determining the size, localization of the Peyronie plaque, its extent, presence/absence of narrowing, type of curvature are among the main tasks of physical examination. Multiple Peyronie plaques are usually located on opposite sides of the penis. The consistency of plaques varies from soft, which is found in the early stages of the disease, to calcified or even ossified, which is found later with the progression of the disease. Formation of the chondroid/osteoid tissue is an unfavorable prognostic sign of the disease, and therefore determining the consistency of plaques is an important diagnostic technique. In combination with other diagnostic methods, photofixation (autofixation) of penis curvature in both the anterior and lateral planes makes it possible to determine the angle, the surface of the penis curvature (ventral, dorsal, lateral) and its localization relative to the penis longitudinal axis. Measurement of the degree of penis curvature can also be performed on standard photographs using two intersecting lines (A and B) passing through the centers of the distal and penis proximal rods, as well as using a special smartphone application – University of Washington Peyronie's Examination Network [40]. In 70 % of patients with PD, there is objectively a shortening of the penis, which can reach 10 cm, most often it does not exceed 1 cm [39].

When conducting differential diagnosis, it is necessary to recognize diseases in the clinical picture of which there is a curvature/deformation of the penis. If we turn to the list of diseases, penis curvature can occur with developmental abnormalities, dorsal vein thrombosis, posttraumatic cavernous fibrosis, secondary syphilitic lesion, epithelial sarcoma, and sometimes with metastases of malignant tumors from other organs and systems. Laboratory tests are not required to diagnose PD, although, given the link between PD and systemic diseases, including hypogenitalism, chronic hyperglycemia and cardiovascular diseases, screening and examination of these conditions in men may be justified. You also need to get information about previously conducted treatment measures for PD.

PD can be diagnosed by palpation of penis plaques, however, changes in the septum, intracavernous and ventral tunica albugineas of the cavernous bodies cannot be detected. Ultrasound examination, including pharmaco-Dopplerography of penis vessels, is a valuable method in the diagnosis of penis diseases, allowing to determine their early forms and identify non-palpable lesions, the degree of fibrosis and assess the condition of blood vessels [41]. In PD, the method is used not only to confirm the diagnosis; in some cases, penile lesions can only be identified by ultrasound. Uncalcified Peyronie plaques on ultrasound are isoechogenic or hyperechogenic compared to the tunica albuginea. With focal thickening of the pericavernous tissue, plaques are hypoechoic, which is rare. Ultrasonography in shades of gray allows to recognize the involvement of plaques in penis septum. Ultrasound shows 100 % sensitivity in detecting and measuring coarse calcifications in the Peyronie plaque. Peyronie plaques are more often located on the dorsal side of the penis, but they can also be found ventrally or, less often, in other places [41]. Penis pharmaco-Dopplerography allows to determine: the angle of curvature, the shape of deformation, the functional parameters of vascular blood flow and predict the necessary surgical intervention. The assessment of the state of the penile vascular bed with the determination of the erectile response to the injection of a pharmacological vasoactive drug (papaverine, prostaglandin or TriMix, including papaverine, phentolamine and prostaglandin E1) is carried out after achieving a full erection [41]. If necessary, compression of the penis at the base is used to increase the rigidity of the penis and revise the dose of the vasoactive drug. In some patients, under direct observation a significant psychogenic inhibition of the erectile response may occur [41]. The minimum dose is the administration of 10 μg of prostaglandin E1 (caverject, alprostadil). On MRI, plaques look like hypointensive areas of thickening in the tunica albuginea in both T1 and T2-weighted images. Calcification of Peyronie's plaques is better manifested on ultrasound than on MRI [41]. Magnetic resonance imaging and computed tomography, as well as sonoelastography, cavernosography, and scintigraphy, are not routine methods used in clinical practice for the diagnosis of PD.

GENERAL PRINCIPLES OF TREATMENT

There is no adequate universally recognized treatment regimen for PD, so the problem of effective treatment of PD remains a very difficult task. As the evidence base expanded, the range of surgical and non-surgical options for PD patients narrowed. Conservative therapy is indicated for patients in the first phase of the pathological process progression, with moderate penis deviation, small size of the Peyronie plaque (up to 1 cm). Complex drug therapy is considered as a first-line therapy as an additional way to relieve pain, prevent disease progression in patients with contraindications or unwillingness to perform surgical correction of deviation. In this situation, patients are offered several treatment options, including oral therapy, injections into the Peyronie plaque, remote low-energy shockwave therapy, etc. Due to the fact that the results of scientific research on the conservative treatment of PD are contradictory, experts from the European Association of Urology (EAU; 2021) and the American Association of Urology (AUA; 2021) do not give recommendations on its use in routine clinical practice [39]. The EAU task force (2021) does not support the appointment of oral therapy for PD, including pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium paraaminobenzoate (potaba), omega-3 fatty acids, a combination of vitamin E and L-carnitine, due to the lack of their proven effectiveness [39]. The clinical feasibility of prescribing of above mentioned drugs to patients with PD may be limited by the manifestation of side effects; in particular, high doses of vitamin E can lead to cardiovascular disorders. Even in the absence of adverse events from the use of these drugs, inadequate treatment may lead to the later appointment of other more effective methods. The options for conservative treatment in the active phase of the disease, which have a strong evidence level, include only the use of nonsteroidal anti-inflammatory drugs (NSAIDs) (diclofenac, indomethacin in candles up to 100 mg) in order to relieve pain and low-energy shockwave therapy (LEST) [39]. LEST can be used only in the acute phase when there is no plaque: it does not lead to lysis of the Peyronie plaque, it only contributes to a faster relief of pain syndrome.

The scientific literature has published positive results of the effective use of NSAIDs, type 5 phosphodiesterase inhibitors, enzymes (collagenase, etc.), verapamil, nicardipine, interferon (IFN) alpha-2b, hyaluronic acid, botulinum toxin in the treatment of Peyronie's disease [40]. Intralesional injections may be offered to patients who refuse surgical treatment. Even F.G. de La Peyronie himself was the first to use mercury and thermal mineral water (holy water of Bareges) locally to treat plaques, eventually reporting efficacy with regular use of mineral water [41]. In 1901 W.J. Walsham and W.G. Spencer were the first to inject mercury and iodide directly into the plaques on the penis, trying to dissolve them [42]. Modern injectable agents can be divided into two groups, namely anti-inflammatory/proliferative agents and lytic agents. In addition to the above, there is evidence of a positive effect of intraocular administration of clostridial collagenas-

es, purified Clostridium histiolytica collagenase (0.58 mg with a difference of 24–72 hours every 6 weeks for 4 cycles) on reducing the degree of penile deviation (in 32–42.9 %) [43]. Clostridial collagenase became the first treatment for PD approved by the U.S. Food and Drug Administration (FDA) in 2013 [41]. Collagenase is injected directly into the primary plaque at the point of maximum bending of the penis, using only one puncture point to deliver the drug. Injections into the plaque (5×10^6 units of IFN-α-2b in 10 ml of saline solution 2 times a week for 12 weeks) can reduce the penile curvature, the size of the plaque and its density, as well as pain compared with placebo, therefore IFN-α-2b is recommended for the treatment of PD in the second stable phase [39].

Traction therapy of penis (> 5 hours a day for 6 months) or devices for vacuum erection (promotes the expansion of the cavernous sinuses) can be used as monotherapy or in combination with other treatment methods to reduce the penile deviation, however, the «promising» effectiveness has yet to be proven [43].

Surgical correction of PD with or without prosthetics remains the main method of PD treatment and the gold standard for correction of penile deformation [44]. No surgical method has been singled out as the standard of medical care. Surgical operations performed to correct penile deviation are divided into interventions performed without preservation (operations with resection on the convex side of the tunica albuginea of the penis – Nessbit, Essed – Schroeder, STAGE, etc.) and with preservation of the length of the penis (operations on the concave side of the tunica albuginea using a graft), as well as operations with simultaneous the installation of penile implants with or without lengthening of the penis in the presence of ED [44]. The patient should understand that the purpose of the operation is to make his penis "functionally straightened"; in clinical practice, after most interventions, there is a penis residual deviation of more or less 20°. All surgical correction procedures involve some loss of length. Based on the opinion of experts from the Russian and European Associations of Urologists, it is recommended that clinicians evaluate and begin surgical treatment of patients with PD only if they have sufficient experience and the medical institution has the appropriate technological capabilities [45, 46]. In the stable stage of the disease, the formation of further surgical intervention tactics depends on the presence/ absence of ED, the effectiveness of previously performed conservative therapy, the initial erectile status of the patient, the initial penile length / thickness, the angle and the presence of complex forms of penile deviation. Important criteria influencing the choice of surgery for PD are the surgeon's experience and the patient's preference [45, 46].

Shortening methods of surgical correction include operations with and without opening the tunica albuginea (plication techniques). The first method (with opening of the tunica albuginea) includes the Nesbit surgery, Nesbit – Saalfeld (longitudinal incisions no more than 1 cm long on the curved side of the tunica albuginea of the penis and suturing in the transverse direction), Nesbit – Lemberger (longitudinal incision on the curved side of the tunica albuginea of the penis with suturing in the transverse direction), Nesbit – Hellstrom (excision of several flaps depending on the degree of curvature), Nesbit – Yachia. The second method (without opening the tunica albuginea or plication techniques) includes Nesbit – Shcheplev surgery, Essed – Schroder (invagination of the tunica albuginea using screwing seams), Nesbit – Lue [45].

The advantages of these surgery include the straightening of the penis (it is possible to achieve in 80 % of patients), a low incidence of recurrences of curvature, ED and decreased sensitivity [45]. A significant disadvantage is that 85 % of patients after Nesbit surgery have a shortening of the penis; at the same time, it does not exceed 1–1.5 cm and does not lead to a significant violation of sexual function. Shortening techniques should be the method of choice and be performed in patients with PD and a curvature angle of less than 45° [45].

Tunica albuginea lengthen surgery are preferred in patients with severe shortening of the penis, pronounced curvature and/or complex deformations (like an hourglass or screw), but without the initial ED. A curvature of more than 60° is considered to be pronounced. An important aspect when performing lengthening operations on the penis is the dissection of the Peyronie plaque along the line of the maximum angle of curvature. Complete removal or excision of the Peyronie plaque is associated with a high rate of ED due to the development of venous leakage, but in the case of severe calcification, partial excision is acceptable. It is necessary to inform patients about the significant risk of ED development up to 50 % after surgery [45]. The risk of shortening can be minimized by penis stretching. No less significant is the characteristic of the material used to replace the tunica albuginea defect. Traditionally, grafts are the main material. There are four types of grafts: autologous transplants from the patient himself (dermis, vein, temporal fascia, broad fascia, tunica albuginea and cheek mucosa); allografts from a cadaveric donor (pericardium, broad fascia and dura mater); xenografts (taken from various animal tissues – bovine pericardium, submucosal layer of pig intestine, bovine and pig dermis, horse collagen matrix); synthetic grafts [47, 48]. Synthetic grafts are not recommended for use in PD [39]. For more than forty years, it has been proposed to use the cheek mucosa as an autologous material during reconstructive urological operations, including for penis deformation correction in PD [47, 48]. Substitutive corporoplasty allows to achieve satisfactory aesthetic and functional results in 90 % of patients and is the preferred method for curvature angles of more than 45–90° and significant size of the Peyronie plaque.

In patients with Peyronie's disease and ED, with the ineffectiveness of pharmacotherapy and severe penile deformation, implantation of penile prostheses with additional techniques (modeling, plication, dissection or excision of plaque with transplant surgery) is indicated [39, 49]. A strict program of postoperative rehabilitation reduces the risk of recurrence of penis curvature and shortening.

THE MAIN POINTS OF THE LECTURE

Peyronie's disease has been haunting humanity for centuries.

The key to successful treatment of the disease is the knowledge underlying its pathophysiology, which is still not fully understood, and the lack of such knowledge leads to the inability to prevent the onset and progression of the disease, which makes fibroplastic induration of penis difficult to treat the disease. Perhaps a vital part of the underlying mechanism is still eluding us, and when it is discovered, it will allow us to differentiate patients whose disease can resolve spontaneously from those whose disease can progress.

The main focus of treatment should be on relieving acute pain and restoring sexual function by reducing penile curvature and associated erectile dysfunction.

Many of the proposed conservative treatment options have either failed or produced contradictory results. NSAIDs and LEST are indicated for the treatment of penile pain syndrome, but should not be used to eliminate penis deformation/curvature or Peyronie plaque.

Intralesional injection therapy IFN-α-2b and clostridial collagenase are recommended for the treatment of PD in the second stable phase in specially selected patients.

Surgery to correct penile deformation in PD with an emphasis on preventing organ length loss remains a difficult task, despite the fact that various techniques have appeared over the past few years. Penis reconstructive surgery is mainly based on the restoration of the functional state of the organ, that is, its straightening while maintaining sufficient rigidity and the possibility of sexual intercourse.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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