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ECTOPIC MINERAL FORMATION IN THE PROSTATE GLAND

Summary. This work analyzes the data of contemporary scientific literature regarding the ectopic mineralization in the prostate gland, its pathogenetic features are considered. The scientific literature of recent decades gives grounds to assert that the processes of concrement formation in the prostate gland are influenced by many factors, pathological mineralization can be realized by different mechanisms. They include chronic inflammation, stagnation fractions in gland, reflux of urine from the urethra at intravesicle obstruction, malformation of prostate and seminal vesicles, specific inflammation, polymorphism of gene protein inhibitors of calcification. These mechanisms are interconnected, each of them may participate in the overall development of concrement formation in the prostate. In recent years, due to improved instrumental diagnosis we observe a significant increase of the number of patients, who were found with pathogenic prostate gland bioliths, which requires more detailed and in-depth study of the mechanisms of mineral formation in the prostate.
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Москаленко Р.А., Романюк А.М., Закорко І.-М.С., Піддубний А.М. Ектопічне мінералоутворення в передміхуровій залозі.
Резюме. У роботі на основі аналізу даних сучасної наукової літератури встановлено, що процеси ектопічного мінералоутворення в передміхуровій залозі можуть реалізовуватися через вплив різних етіологічних факторів. До них належать хронічне запалення, застійні явища у залозі, рефлюкс сечі з сечівника при інтравезикулярній обструкції, мальформації простати та сім'яних міхурців, специфічне запалення, поліморфізм генів білків-інгібіторів кальцифікації. Механізми ектопічної мінералізації взаємопов'язані, кожний з них може брати участь у загальному розвитку конкрементоутворення в передміхуровій залозі. За останні роки, у зв'язку з покращенням інструментальної діагностики відбулося значне зростання числа хворих, у яких були виявлені патогенні біоліти передміхурової залози, що потребує більш детального і поглибленого вивчення механізмів мінералоутворення у передміхуровій залозі.
Ключові слова: простата, ектопічне мінералоутворення, конкременти, патогенез.

Introduction

The human body is a complex system of organic and inorganic substances that are in balance. One of the consequences of the imbalance is ectopic biomineralisaton in human tissues and organs. Genetically pathogenic mineral aggregates are the "disease" of the body (Голованова О.А., 2003). The response of a living organism to the external pressure is the change of concentration of components of physiological fluids, the structure destruction of epithelial sheets and as a result, changing the parameters of their moisture, and the disruption in the mechanism of synthesis of inhibitors-substances that inhibit the growth of concretions (Giachelli C.M., 1999).

The aim of this work is to conduct data analysis of scientific literature on ectopic mineral formation in the prostate to detect etiopathogenetic features of prostate stones and effective ways to treat and prevent their formation.

Aggregates of organic mineral are essential elements of the structure of many systems of living organisms. Together with genetically caused mineral formation (bone, teeth, etc.) pathogen bioliths are widespread. Inparticulary their number includes kidney, gallstones, products of heart valves calcification and also parenchymal organs stones, including prostate (Tasci A.I. et al., 2009).

Difficulties of studying pathogens minerals are connected with complex material and elemental composition of stones, containing both mineral (often very poorly crystallized) and organic components, which are very difficult to separate (Голованова О.А., 2003). In addition, mechanisms of formation and growth of crystalline phases that make up the stones have complex relationships that are currently insufficiently understood (Dyer R.B. et al., 1998). Recently the incidence of inflammatory diseases of male genital organs has increased. One of the first places among these diseases takes non-

specific chronic prostatitis, and its subclinical forms have predominated (Арнольди Э.К., 1999).

One of the results of such pathomorphosis is stone formation in the parenchyma of prostate (PG). Widespread application of ultrasound research methods into clinical practice (ultrasound) led to the increase of the frequency of prostatolitiasis detection (Судариков И.В., 1994).

The first notification of stones in the prostate gland was made by Donatus in 1586. Prostatolitiasis was redescribed by English doctor Paul in 1737. In 1861 Henry Thompson described starch corpuscles (corpora amilacia) in prostatic glands and he was the first who suggested the hypothesis, that these cells are calculus predecessors (Малков А.Л. и соавт., 2006).

Small stones in the prostate gland are usually asymptomatic and they are often accidentally detected at radiography, ultrasound (sonography), prostatectomy and histological examination. Big and infected stones usually cause a lot of patient complaints. The most frequent manifestation of stone formation in PG is the pain. Patients complain of pain in the perineum, lower back, spine, region above pubis, which irradiates to the genitals, inner hip area. A characteristic feature of this pain is its increase during seating on a hard surface, sexual intercourse, or after a massage of PG, jog drive (Стецишин З.В и соавт., 2004). One of the manifestations of stones in the PG can be hidden haemospermia, which is manifested by the patient himself or by laboratory study of ejaculate. Dysuric phenomena are less common from frequent urination till the development of complete intravesicular obstruction (Арнольди Э. К., 1999).

Researchers' views for the etiology of stones in PG are inconsistent. Most authors consider that the occurrence of stones is associated with prolonged inflammation in the prostate gland and they review them as a complication of chronic prostatitis (Судариков И.В., 1994). Research shows that prostate stones are a common disease (if it's studied with ultrasound research): by the analysis of ultrasound results of 990 patients aged 26 to 83, hyperechoic prostate inclusion detected in 472 (48%) patients (Артеменко О.В., 2011). In the work of J.Hee Suh's et al. (2008) 298 cases of radical prostatectomy and cystoprostatectomy were analyzed. Prostate calcificates were detected in 88.6% patients, seminal vesicles – in 58.1%, ejaculatory duct – in 17.1%.

In another work it is reported that by examining 600 patients with chronic prostatitis, calculi were found in 140 men (23%) at the age from 21 to 69. Duration of disease varied from 6 months to 25 years, averaging 8.8 years (Судариков И.В., 1994).

C.T.Ramirez et al. (1980) distinguish two groups of etiological factors that cause the formation of stones in the prostate. The first group promotes the development of very small, often microscopic stones, which occur in the prostate gland of almost all elderly men. These concretions, stones, which were formed in particles, are called primary (endogenous). Primary prostatoliths are macroscopically oval or round shape, from 0.5 to 4 mm in diameter (rarely more), of dense texture, with smooth, yellow-brown or bright reddish-brown color. By cutting them in half, we can see nucleus and one or more concentric layers. The structure of the original stone is a compact core of hydroxyapatite in combination with organic matter (proteins, cholesterol) in a greater or lesser proportion, and the peripheral layers (concentric, rarely lobed), which consist of apatite (Закорко І-М.С та співавт., 2011). Amyloid corpuscles, which are in ferruginous acinuses, are impregnanted by inorganic components, mainly by calcium salts. Further accumulation of these substances occurs until the concretions become thick, opaque and completely visible to the naked eye at sections. There are various theories that explain this transformation. According to some researchers, amyloid corpuscles act as extraneous objects that irritate the mucous membrane, leading to deposition of calcium salts (Судариков И.В., 1994). Other researchers link the accumulation of calcium salts with violation of surface tension on the border of amyloid corpuscles of the surrounding fluid (Sang-Wohn J. et al., 2009).

Stones, wich were formed in the ducts of the primary components, which penetrated to them from the outside are called secondary (exogenous) prostatolits (Ramirez C.T et al., 1980). These stones are of various shapes, usually round, with fewer crystalline substance. They have a nucleus that consists mainly of oxalate, in structure similar to concrements, that are formed in the kidneys and ureters (Романюк А.М. и соавт., 2011). At the periphery they are composed of alternating layers of apatite, and oxalate. When stones are closely facing to each other, they get facet surface. Sometimes these stones can cause frequent recurrence of inflammatory diseases, as they contain pathogens that are fully protected from exposure with antimicrobial agents (Горпинченко И.И. и соавт., 1992).

Pathogenic bioliths in the prostate may also be formed at specific inflammation – tuberculosis (MacKenzie D., Seng M.I, 1920). However, they contain mostly salts of magnesium, calcium and sodium. Inorganic component was only half of the total mass of stones. Analysis of the prostate secretion has found that the ratio of the concentration of calcium ions to magnesium ions is 3:1.

The phenomena of ectopic mineral formation in the prostate gland also observed at the background of a malignant tumor process (Yuen H.F. et al., 2010). Recently the calcification phenomenon of multipotent capillary endothelium of the tumor in the prostate gland has been found (Duddley A.C. et al., 2008). Ectopic bone and cartilage tissues, cells like osteoklast, calcified vessels cells were previously described by diseases of the vascular wall (Wat-

son K.E. et al., 1994;Tintut Y. et al., 2003). For example, calcification in blood vessels is typical for the middle layer, it develops around atherosclerotic plaques (Moe S.M. et al., 2004). Areas of pathological calcification are enriched by newly formed vessels that proliferate around calcium deposits (Johnson R.S. et al, 2006). In contrast to the processes of calcification in the wall of the heart valves and arteries, where mineralization develops in the extracellular matrix and around the smooth myocytes, calcificates processes occur mainly at luminal capillaries surface by prostate cancer (Duddley A.C. et al., 2008). In case of prostate cancer endothelial tumor cells undergo atypical epithelial-mesenchymal transformation with the formation of bone-like tissue, that's why some authors suggest that the osteogenic microenvironment facilitates prostate cancer metastasis into the bones (Chung L.W., 2003, Edlund M. et al., 2004).

Violation of embryonic prostate and seminal vesicles (Muller ducts, urogenital sinus) can contribute the development of ectopic mineral formation in the prostate gland, such as prostatic utricle enlargement, cysts, that lead to stagnation of secretions in the gland or urine reflux (Lin J. et al, 2011).

Publications of recent years associate the processes of bioliths formation with the gene polymorphism of matrix protein MGP (matrix Gla protein) (Gao B. et al, 2007). Matrix protein MGP is metal protease and refers to factors that protect tissue from excessive mineralization, mainly from the deposition of calcium salts (Kobayashi N. et al., 2004). Protein MGP is formed by posttranslation modification with vitamin K-dependent γ-glutamate decarboxylase through γ-carboxylation of glutamic acid (Herrmann S-M. et al, 2000). This protein contains 5 residues of γ-carboxyglutamic acid, 3 phosphorylated serine residues, that take place in binding of calcium ions and crystals, bone forming proteins (bone morphogenetic proteins) (Shulgers L.J. et al., 2007). The importance of protein MGP in preventing of ectopic mineralization of soft tissues is clearly illustrated by the example of experimental model of mgp-knockout mouse, which have intense vascular calcification, which leads to rupture of the vascular wall and early death. J.O'Young et al. (2011) suggest that MGP prevents ectopic mineralization, by stopping the growth of hydroxyapatite crystals, but the exact mechanism of matrix protein influence isn't known (Proodfoot D, Shanahan C.M., 2006).

V.J.Simonov et al. (2008) studied 17 patients with stones of prostate gland. The program of study included microscopic and microbiological study of the first and the second portions of urine, a swab from the urethra, the discharge from the urethra (if available), prostatic secretions, urine after prostatic massage, ejaculate. From 17 patients with stones of prostate tissue infection was detected in 8 (St. epidermidis – 3; Proteus – 3, E coli – 2), the presence of infection in the concretions – only in 4 patients. Thus, the infection of the prostate gland was observed significantly more frequently than prostate stones that may indicate a relatively large value of other (non-infectious) factors in the etiology of PG stones.

In a clinical study (Малков А.Л. и соавт, 2006) treatment of 64 patients with chronic calculous prostatitis was conducted. The age of patients varied from 24 to 63, with the duration of the pathological process from 3 to 22 years. According to the ultrasound, the size of concretions were from 0.2 to 0.7 cm. An important detail of this study is that in 48 (66%) patients prostatolithias ran at the background of violation of metabolism uric acid and combined with urate nephrolithiasis.

I.I.Gorpinchenko et al. (1992) examined 350 patients with chronic prostatitis aged 21 to 71 in average 48 ± 12 years old. In 48 (13.7%) of them stones were found in the PG. Duration of illness ranged from 6 months to 35 years, in average of 10,2±7,5 years. At admission to the clinic 14 (71%) patients complained of pain. The pain of 66% of patients localized in crotch area, 30% – in the area of the pubis. Increased pain during or after ejaculation was noted in 36% of studied patients. Impurity blood levels in semen were revealed in 81 (23%) patients. In 24 patients (50%) dysuric phenomena were observed. Despite the fact that 38 (79%) patients felt pain in PG during palpation, the focus changes during the finger examination were detected only in 15 (31%). By a laboratory study of PG secretion increased amount of leukocytes was found in 6 (75%) patients, erythrocytes (more than 10 in the microscope field of view) – in 27 (56%) patients. Pathogenic microflora was determined in a PG secretion in 37 (77%) of studied.

The most informative diagnostic method was ultrasound: one concrement detected in 17 (36%) patients, two – in 15 (31%), three – in 3 (6%). Multiple stones were observed in 13 (27%) patients. In the right lobe of PG stones localized in 12 (25%), in the left one – in 11 (23%), in the middle one – in 7 (14.5%) and in both lobes – in 18 (37.5%) men. The sizes of stones ranged from 0.2 to 1.5 cm, but most often (32 patients, 66.6%) concretions diameter was 0.5-0.8 cm (Горпинченко И.И. и соавт., 1992).

Comparative studies of quality characteristics of spermatozoa showed that in patients with chronic prostatitis, complicated calculus, an increased number of dead and fixed spermatozoa was found and a significant increase of their abnormal forms compared with the same parameters in patients without stones in the prostate gland (Арнольди Э.К., 1999).

Thus, the increase of the number of red blood cells in prostatic secretions and in ejaculate (gemospermy) in patients with chronic prostatitis, complicated by calculus, can serve as an additional diagnostic test of the stone presence.

The presence of stones substantially intensifies the course of inflammation in the prostate gland

(Малков А.Л. и соавт., 2006). Prostatoliths that are in acinuses and ducts, make a traumatic effects on surrounding tissue, disrupting the microcirculation, maintain a chronic inflammation due to contamination by microorganisms that remain after antibiotic therapy (Стецишин З.В и соавт., 2004).

Conclusion

The scientific literature of recent decades gives grounds to assert that the processes of concrement formation in the prostate gland are influenced by many factors, pathological mineralization can be realized by different mechanisms. They include chronic inflammation, stagnation fractions in gland, reflux of urine from the urethra at intravesicle obstruction, malformation of prostate and seminal vesicles, specific inflammation, polymorphism of gene protein inhibitors of calcification. These mechanisms are interconnected, each of them may participate in the overall development of concrement formation in the prostate.

In recent years, due to improved instrumental diagnosis we observe a significant increase of the number of patients, who were found with pathogenic prostate gland bioliths, which requires more detailed and in-depth study of the mechanisms of mineral formation in the prostate.

Prospects for further research

In further work we plan to study the mechanisms of prostatoliths formation by various diseases of the prostate.

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Москаленко Р.А., Романюк А.Н., Закорко И.-М.С., Пиддубный А.М. Эктопическое минералообразование в предстательной железе.

Резюме. В настоящей работе на основании анализа данных современной научной литературы установлено, что процессы эктопического минералообразования в предстательной железе могут реализовываться посредством воздействия различных этиологических факторов. К ним относятся хроническое воспаление, застойные явления в железе, рефлюкс мочи из уретры при интравезикальной обструкции, мальформации предстательной железы и семенных пузырьков, специфическое воспаление, полиморфизм генов белков-ингибиторов кальцификации. Механизмы эктопической минерализации взаимосвязаны, каждый из них может принимать участие в общем развитии конкрементообразования в предстательной железе. В связи с улучшением инструментальной диагностики в последние годы произошло значительное увеличение количества пациентов, у которых были выявлены конкременты предстательной железы, что требует более детального и углубленного изучения причин и механизмов их развития

Ключевые слова: предстательная железа, эктопическая минерализация, конкременты, патогенез.