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MODERN ASPECTS OF PATHOGENESIS, DIAGNOSIS, TREATMENT AND MOLECULAR GENETIC BASIS OF UROLITHIASIS IN CHILDREN (LITERATURE REVIEW)

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СОВРЕМЕННЫЕ АСПЕКТЫ ПАТОГЕНЕЗА, ДИАГНОСТИКИ, ЛЕЧЕНИЯ И МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ ОСНОВЫ МОЧЕКАМЕННОЙ БОЛЕЗНИ У ДЕТЕЙ (ОБЗОР ЛИТЕРАТУРЫ)

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Summary. Urolithiasis in children is a polyetiological disease, the formation of which is influenced by various factors: exogenous and endogenous. As exogenous risk factors for the development of the disease are identified such as: environmental disorders, increased concentration of calcium salts and heavy metals in drinking water, poor quality, excessive consumption of vegetable and protein food, high level of urbanisation, active migration of population, climate change, with a shift towards global warming. Endogenous factors also play an important role in the pathogenesis of USD development: anomalies of development of the urinary system, metabolic diseases, genetic predisposition.

Key words: *urolithiasis in children, molecular genetic basis, diagnostics.*

Резюме. Мочекаменная болезнь у детей является полиэтиологичным заболеванием, на формирование которого оказывают влияние различные факторы: экзогенные и эндогенные. В качестве экзогенных факторов риска развития заболевания выделяют такие, как: нарушение экологической обстановки, повышенная концентрация солей кальция и тяжелых металлов в питьевой воде, некачественное, избыточное потребление растительной и белковой пищи, высокий уровень урбанизации, активная миграция населения, изменение климата со сдвигом в сторону глобального потепления. В патогенезе развития УЗД важную роль играют также эндогенные факторы: аномалии развития мочевыделительной системы, болезни обмена веществ, генетическая предрасположенность.

Ключевые слова: *мочекаменная болезнь у детей, молекулярно-генетическая основа, диагностика.*

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To diagnose urolithiasis in children, a complex of clinical, laboratory and instrumental methods of investigation is used, each of which has its advantages and disadvantages. Immunogenetic method of research has a certain superiority among other methods of research, because it has the ability to diagnose urolithiasis at the preclinical stage, while other diagnostic methods work in the presence of uroliths in the urinary tract.

Insufficient study of genetic risk factors for the development of recurrent USD in children necessitates further research.

Worldwide, epidemiological studies have shown in recent years that there has been a significant increase in the incidence of urinary system diseases in children. According to the World Health Organisation (WHO), the incidence of urolithiasis in children has increased by 6-10% annually over the

past 20 years in the United States, with an estimated current average annual incidence of 36 to 57 per 100,000 children per year. Because up to 40% in children are diagnosed incidentally (e.g., after a first or recurrent urinary tract infection) because of the high proportion of nonspecific symptoms, the exact incidence may be underestimated. To date, the increasing incidence of urolithiasis, especially among children, insufficient study of pathogenetic mechanisms, features of the clinical course, frequent recurrences and complications make it necessary to improve its early diagnosis and surgical tactics. Globally, special attention is paid to scientific research on the study of etiology, risk factors, mechanisms of development, diagnosis and differential diagnosis, course of paediatric diseases, in particular urolithiasis, as well as effective methods of diagnosis and treatment.

The cause of urolithiasis can be identified in 67–92.6% of cases. Currently, two groups of factors of urolithiasis development are distinguished: exogenous and endogenous [29].

Exogenous factors include ecology, parental lifestyle, aggravated gynaecological anamnesis, living in a hot climate, race, sex and age of the child, intake of food rich in animal protein, high-calorie diet, taking medications. Endogenous factors include anomalies of the structure of the organs of the urinary system, urinary infection, metabolic disorders, heredity and genetic predisposition [3, 7, 9, 15, 23, 26].

These are factors that are well studied and are not questionable. However, it is important to note that many researchers in recent years have come to the conclusion that genetic predisposition to metabolic disorders related to the metabolism of stone-forming substances is the main determinant of urolithiasis development, while environmental and dietary factors, which play an important role in the development of urolithiasis in adults, remain insignificant in children [27].

Such seemingly unimportant risk factors as: the environmental situation in the place of direct residence of patient's families, parents' lifestyle, aggravated gynaecological history of the future mother and the nature of intercurrent diseases of the child can lead in some cases to the formation of various anomalies of the urinary system in children, disturbance of metabolism of stone-forming substances and development of a serious disease - urolithiasis.

The hereditary factor in the development of urolithiasis is more and more widely discussed in modern literature. The family history of the disease is traced in 46–83% of cases and is least pronounced in European countries (12–33% of observations); in North American children this figure is 33–69%, the highest frequency is observed in children from Asian countries (up to 83%). The role of genetic factors in the development of polygenically inherited membranopathies, congenital and acquired enzymopathies, tubulopathies and metabolic nephropathies, as well as some monogenic forms of lithogenic metabolic disorders has been proved [4, 5, 9, 27].

Molecular genetic basis of urolithiasis. Modern urology has a significant arsenal of methods to rid most patients of kidney and urinary tract stones. However, removing a stone does not mean getting rid of urolithiasis. That is why the problems of metaphylaxis (prevention of recurrence) of urolithiasis are extremely important. Treatment of most conditions in which stones form in the urinary tract is currently based mainly on symptoms rather than causes. In this regard, it seems relevant to study the genotype distribution of polymorphic marker polymorphisms of the genes for vitamin D receptor, osteopontin, urokinase, fetuin-A, interleukin-1beta, and interleukin-18 in children with and without urolithiasis [10, 11].

A complete understanding of the molecular causes of these conditions, including the identification of mutant genes and their gene products should lead to more rational treatment protocols. Of great importance in the diagnosis of urolithiasis is the identification of the degree of involvement of genetic factors. Research results and literature data have shown that hereditary predisposition in combination with environmental factors has a significant influence on the occurrence of metabolic disorders characteristic of urolithiasis [17, 20, 28, 29, 30].

The realisation of hereditary predisposition to urolithiasis is associated with genetically determined structural and functional features of metabolism, neurohumoral regulation, and local factors. In their epidemiological or clinical studies, foreign scientists note the participation of genetic factors in the occurrence of urolithiasis, which suggests the existence of specific genes responsible for the occurrence of urolithiasis. One of the USD candidate genes is the Vitamin D Receptor gene [27, 28, 29, 30].

Vitamin D receptor is encoded by the VDR gene, which is characterised by genetic polymorphism, i.e. the existence of different allelic variants of this gene in the population. The most significant polymorphisms of the VDR gene involved in disease development were: Bsm I, Fok I, Taq I. Several studies have linked VDR gene polymorphisms with urolithiasis. Published data demonstrating the significance of ApaIAA genotype, which determines sensitivity to vitamin D, in the development of calcium stones in the urinary tract [Ozkaya O., 2003]. It is also reported about the greater frequency of occurrence of

HLA genes B13, B22 and B35 in patients with urolithiasis compared to healthy individuals [Tiktinsky O.L., 2000]. Also, candidate genes are osteopontin, urokinase, fetuin-A, interleukin-1beta, interleukin-18.

Studies conducted by foreign scientists have shown that metabolic disorders of phosphorus metabolism lead to hypophosphatemia and often associated hypercalciuria and urolithiasis. Such a disorder was found to be associated with two different heterozygous mutations in a renal sodium phosphate transport protein encoded as the *NPT2a* gene. Each of the disrupted genes was identified. Such abnormalities were identified in patients with recurrent urolithiasis and decreased renal reabsorption of phosphate. Interestingly, other genetic forms of urolithiasis associated with hypophosphatemia have been established without the presence of mutations in the *NPT2a* gene of the same name. All of these disorders have very high levels of the active product of vitamin D by the endocrine system, 1,25 dihydroxyvitamin D. These high levels of 1,25 dihydroxyvitamin D may contribute to a higher than normal efficiency of calcium absorption through the gastrointestinal tract and reduced synthesis and secretion of parathyroid hormone. Such physiological changes in calcium homeostasis speak in favour of hypercalciuria and thus may contribute to kidney stone formation [1, 2].

Despite many population-based molecular genetic studies, the molecular genetic markers of urolithiasis in children are still poorly understood. The choice of nutritional therapy as well as the efficacy of nutritional therapy depending on the genetic status of the patient is also insufficiently studied. Pharmacogenetic aspects of urolithiasis, such as the choice of pharmacological agents for conservative treatment and metaphylaxis of urolithiasis depending on genetically determined functional features of metabolism are also insufficiently studied [8, 9, 28].

The method of predicting the occurrence of urolithiasis based on the detection of molecular genetic markers on the basis of DNA analysis has certain and significant advantages. The biochemical method of determining mineral metabolism disorders used for these purposes allows, first of all, to diagnose the existing disease, i.e. it is effective in a sufficiently long pathological process. Meanwhile, it has been established that even in the presence of an obvious disease, biochemical changes are detected only in half to two thirds of subjects [17, 29, 30].

Predisposition to a disease can be established by molecular genetic method in the absence of any clinical or biochemical manifestations, i.e. at the earliest preclinical stage of pathology development. Thus, the earlier the presence of a genetic marker is detected, the more reliable and timelier will be the measures to prevent the disease.

In cases of already existing USD disease, the study of association of molecular genetic markers with recurrent forms of urolithiasis, as well as the establishment of pharmacogenetic interactions will contribute to more effective postoperative metaphylaxis of urolithiasis. Reduction in the incidence of urolithiasis due to early effective detection of predisposition to it, as well as more effective postoperative metaphylaxis of urolithiasis will lead to a significant reduction in material costs for the organisation and implementation of treatment measures.

Improved knowledge in the region of molecular mechanisms underlying the formation of urinary constituents such as calcium, oxalates, cystine and uric acid will improve the diagnosis, treatment and prevention of urolithiasis in children. The study of genetic factors will also make it possible to develop therapeutic measures aimed at eliminating the molecular-genetic defect, which will further prevent the formation of kidney stones. The main directions in the study of urolithiasis all over the world are the search for and finding the causes of stone formation, gentle methods of removing concretions and adequate metaphylaxis. In recent years, the accumulation of knowledge in the region of molecular genetics has made it possible to explain the mechanisms of urolithiasis, which has led to a new era of diagnosis and treatment of stones. In contrast to traditional diagnostic methods, the molecular genetic method of predicting the occurrence of urolithiasis makes it possible to identify predisposition to the disease at the preclinical stage at any age, practically from birth, since the genotype of a particular individual does not change during life.

Treatment of most conditions that produce urinary stones is currently based predominantly on symptoms rather than causes. A full understanding of the molecular causes of these conditions, including the identification of mutant genes and their gene products, should lead to more rational treatment protocols. The most significant dramatic change in this direction has come from the identification of gene defects in PG1 (MsC 259900), for which enzyme replacement therapy with liver transplantation has become effective and long-lasting. An extension of this trend, in which all defective genes in urolithiasis are identified, cannot be realised until gene therapy is introduced as a 'routine' procedure in treatment. The correspondence of gene mutations and severe forms of urolithiasis makes prenatal diagnosis possible and promising.

The realisation of hereditary predisposition to urolithiasis is associated with genetically determined structural and functional features of metabolism, neurohumoral regulation, and local factors. In their epidemiological or clinical studies, foreign scientists note the participation of genetic factors in the occurrence of urolithiasis, which suggests the existence of specific genes responsible for the occurrence of urolithiasis. One of the candidate genes for USD is the vitamin D receptor gene.

Vitamin D receptor is encoded by the VDR gene, which is characterised by genetic polymorphism, i.e. the existence of different allelic variants of this gene in the population [Kukes V.G., 2007; Uitterlinden A.G., 2004]. The most significant polymorphisms of the VDR gene involved in the development of diseases were: Bsm I, Fok I, Taq I [Lee B.K., 2001; Uitterlinden A.G., 2004; Bid H.K., 2005]. Several studies have linked VDR gene polymorphism with urolithiasis.

McKusick's On-Line Mendelian Inheritance in Man (OMIM) genetic catalogue has identified more than 30 conditions in which urolithiasis is the main manifestation or contributes as a symptom in the overall manifestation of the disease.

Diseases with renal stone formation range from rare but well understood monogenic conditions such as primary hyperoxaluria to widespread but poorly understood conditions such as familial idiopathic hypercalciuria.

All conditions can be divided into several groups. One group is conditions where the heritable elements are evident and genes have been cloned, mutations identified and causal relationships between genotype and phenotype established (i.e. MsC 102600, 220100, 259900, 260000, 278300, 308000, 311850). The second group - conditions where hereditary manifestations are traceable and genetic bases are assumed from the familial distribution (i.e. MsK 143870, 167030). There is also a group of monogenic diseases, such as autosomal, X-linked, recessive and dominant conditions. Most types of urinary stones are known to form in monogenic diseases, such as calcium oxalate (MSK 259900, 260000), calcium oxalate and calcium phosphate (MSK 300009, 310468, 307800), uric acid and other purines (MSK 102600, 232200, 278300, 308000, 311850), cystine (MSK 220100, 600918).

Determining the genetic contribution to urolithiasis is complicated by its multifactorial nature. This is especially confirmed in the formation of stones composed entirely or partially of calcium oxalate. There are quite a few parameters that contribute to calcium oxalate crystallisation in the kidney or urinary tract, such as high urinary concentration of calcium oxalate and crystallisation promoters (urates) and low concentration of crystallisation inhibitors (citrate, uromodulin (MsK 191845), osteopontin (MsK 166490) and nephrocalcin). Most of these changes are genetically determined or determined by environmental factors.

Oxalate metabolism in healthy individuals is well balanced. Even under normal circumstances, urine is supersaturated with calcium oxalate and, accordingly, small changes in oxalate homeostasis result in an imbalance in favour of crystallisation. If changes in normal metabolism are minor or nonspecific, as in some familial forms of urolithiasis, true signs of heredity may be masked by the influence of environmental factors, making functional or positional cloning difficult.

Genetically determined types of urolithiasis. Primary hyperoxaluria type 1 (PH1) (MSK 259900) is an autosomal recessive disorder of glyoxalate metabolism caused by deficiency of the intermediate metabolic enzyme alanine-glyoxylate aminotransferase in the liver. Also described is a frequent mutation leading not to reduced activity but to reduced compartmentalisation of the enzyme (in mitochondria instead of peroxisomes) G630A. Many other specific mutations have been identified (Gly170Arg, Pro11Leu) and their wide variety has changed aspects of clinical approaches to PG1, especially prenatal diagnosis. Clinically, PG1 is characterised by increased excretion of oxalate and glycolate and chronic accumulation of calcium oxalate in the urinary tract (urolithiasis and nephrolithiasis) or renal parenchyma (nephrocalcinosis). PG1 is a very heterogeneous condition at clinical and molecular levels [S.V. Papizh, L.S. Prichodina et al. 2011]. At the clinical level PG1 is a kidney disease, but at the molecular level it is a liver disease.

The clinical phenotype of the disease is extremely heterogeneous. Some authors have distinguished neonatal, paediatric and adult forms of the disease, which in fact represent a continuum of clinical phenotypes differing in timing and severity of manifestation. The age of onset varies widely, from the 1st year of life to the 7th decade, in most cases before the age of 5 years. In most patients, the disease manifests with either renal colic or asymptomatic marked haematuria developing due to oxalate urolithiasis. The latter along with nephrocalcinosis steadily progresses, leading to the development of renal failure, which turns into uremia and leads to death in the period up to 20 years in 80% of patients. Due to renal failure calcium oxalate can accumulate in almost all tissues of the body (systemic oxalosis).

The most effective method of causal therapy is liver transplantation, which is usually combined with kidney transplantation, replacing biochemically and pathophysiologically defective organs simultaneously. The experience of more than 100 combined liver and kidney transplants for PG1 has been accumulated in medicine. Partial liver transplantation is clinically ineffective. Isolated kidney transplantation improves for a short time and under normal circumstances is not a long-term treatment because it does not eliminate the cause of the disease. Metabolic correction is maximised if liver transplantation is undertaken before terminal renal failure forms, so that kidney transplantation can be avoided. Dietary restrictions of both oxalate and calcium are not effective. In some patients, administration of pharmacological doses of pyridoxine, a cofactor of all aminotransferases resulted in decreased excretion of oxalate. The possibility of gene therapy for this disease is discussed in the literature.

Primary hyperoxaluria type 2 (PH2) (MsK260000) was previously categorised as PH1 because it shares many of the same symptoms. PH2 has milder symptoms than PH1, yet some patients reach end-stage renal failure. Like PG1 PG2 is autosomal recessive, but only at the biochemical level.

PG2 is caused by a deficiency of the intermediate enzyme glyoxylate reductase. In humans, glyoxylate reductase facilitates the conversion of glyoxylate to glycolate. When glyoxylate reductase is deficient, more glyoxylate can be metabolised to oxalate. Glyoxylate, being a reactive molecule, is toxic to tissues, causing changes in a number of enzyme systems. In contrast, glycolate does not have a pronounced toxic effect. Methods of causal therapy include haemodialysis and peritoneal dialysis (less effective) [Bushinsky D.A., Kirn M, 1994].

X-linked recessive nephrolithiasis (MSK 310468), Dent's Disease (MSK 300009), and possibly, Type III hypophosphatemic rickets (MsK 307800) are allelic variants of an X-linked tubular tubular renal disorder characterised by proteinuria (low molecular weight protein), hypercalciuria, nephrocalcinosis, nephrolithiasis and renal failure. Renal deposits consist of calcium phosphate and calcium oxalate. Accumulating evidence shows that X-linked nephrolithiasis, Dent's disease, and type III hypophosphatemic rickets are caused by a mutation in the CLCN5 gene Chr11.22 (MsK 300008).

Lesch-Nyhan syndrome (Lesch-Nyhan), (McK 308000) is an X-linked recessive disease that develops as a result of deficiency of the enzyme hypoxanthine-guanine-phosphoribosyltransferase. The clinical phenotype is heterogeneous. Three clinical forms are distinguished: classical or Lesch-Nyhan disease proper, atypical without CNS lesions, and atypical with CNS lesions. In addition to mental retardation and neurological symptoms, these patients often develop urolithiasis due to increased synthesis and excretion of uric acid. Allopurinol, a xanthine oxidase inhibitor, reduces serum uric acid levels and prevents most of the symptoms associated with hyperuricaemia without affecting neurological symptoms. The greatest therapeutic effect is associated with neurotransmitter drugs (L-5-hydroxytryptophan, CarbiDOPA, LevaDOPA, Tetrabenazine).

Increased phosphoribosyl-pyrophosphate synthetase activity is an X-linked recessive condition in which purine synthesis is increased and gout and uric acid urolithiasis develop. The PRPS1 gene localised in Xq22-q24 (MsK 311850) and the PRPS2 gene in Xp22.3-p22.2 (MsK 311860) are responsible for the development of this condition. The clinical phenotype is heterogeneous: a distinction is made between a more severe paediatric form and a milder adult form.

Xanthinuria (MSK 278300) is an autosomal recessive disorder in which the urinary excretion of xanthine and, to a lesser extent, hypoxanthine is increased. The disease is more common in males. The disease is caused by a deficiency of the enzyme xanthine oxidase (xanthine dehydrogenase), which catalyses the conversion of hypoxanthine to xanthine and then to uric acid. Mutations in the XDN gene localised in chromosome 2p22.3-p22.2 provide this deficiency. The clinical phenotype is heterogeneous. A distinction is made between classical and cofactor-deficient forms. Classical is subdivided into types I and II, but only at the biochemical and not at the clinical level.

Adenine phosphoribosyltransferase deficiency (MsC 102600) is an autosomal recessive disorder manifested by increased synthesis and urinary excretion of 2,8-dihydroxyadenine, which is a poorly soluble compound that readily crystallises in the urine and forms stones. The APRT gene, whose mutations provide this condition, is localised in chromosome 16q22.2-23.2. In most cases, the disease is misdiagnosed as urate lithiasis on the basis of the identical chemical reactivity of uric acid and 2,8-dihydroxyadenine crystals and the X-ray transparency of both types of stones, which is accompanied by the prescription of inadequate therapy.

Cystinuria (ISC 220100) is an inherited kidney disease in which the urinary excretion of cystine, lysine, arginine and ornithine is increased. Cystine is poorly soluble and therefore urinary concretions are easily formed. Genetically, cystinuria is a heterogeneous disease with three variants. Cystinuria

type 1 is caused by a mutation in the CSNU1 gene in chromosome 2q16.3, which results in decreased resorption of cystine and other amino acids. Cystinuria type 2 and cystinuria type 3 are caused by mutations in as yet not precisely defined genes located in chromosome 19q13.1.

The hereditary factor in the development of urolithiasis is increasingly discussed in the current literature. A family history of the disease can be traced in 46–83% of cases and is least pronounced in European countries (12-33% of observations); in North American children it is 33-69%, with the highest frequency in children from Asian countries (up to 83%). The role of genetic factors in the development of polygenically inherited membranopathies, congenital and acquired enzymopathies, tubulopathies and metabolic nephropathies, as well as some monogenic forms of lithogenic metabolic disorders has been proved [4, 5, 9, 27].

The health status of parents, pregnancy and postnatal period also requires attention, since their influence on the increase in the prevalence of anomalies of the urinary system in children has been observed. The somatic and mental state of health has a significant impact on the reproductive potential of the adult population. The dynamics of morbidity of various population groups, during the reforms taking place in our country, has unfavourable tendencies. In spite of the fact that the general morbidity rate in recent years (1991–1999) has increased by only 10.5%, the share of diseases with chronic and recurrent course has significantly increased, and the structure of adult morbidity has changed (the share of diseases of the circulatory system, nervous system, and genitourinary organs has increased).

In this regard, it is relevant to study the distribution of genotypes of polymorphic markers of vitamin D receptor, osteopontin, urokinase, fetuin-A genes in Uzbek children with USD and children without urolithiasis. And on the basis of genetic and biochemical testing data to evaluate the differences in the state of phosphorus-calcium metabolism, as well as oxalate, uric acid and other substances in the group of USD patients.

Vitamin D receptors are encoded by the VDR gene. The VDR gene is characterised by genetic polymorphism, i.e. the existence of different allelic variants of this gene in the population has been revealed. The most significant polymorphisms of the VDR gene involved in the development of these diseases were: Bsm I, Fok I, Taq I [3, 27]. Since the isolation of the VDR gene [6], several genetic studies have linked the VDR gene polymorphism with diseases such as osteoporosis, urolithiasis, hyperparathyroidism, psoriasis, irritable colon syndrome, tuberculosis, CPN, renal osteodystrophy, tumour diseases, periodontal diseases, and various cardiovascular diseases [20, 21, 26, 27].

The prevalence of VDR gene polymorphism has racial-ethnic differences. For example, 15-25% of Americans, Europeans, and Australians have the BB genotype of the Bsm I polymorphic marker of the VDR gene; in contrast, 0-13% of blacks and 1–3% of Asians [17, 30].

A study by Lee et al. examined the association between BP, prevalence of AH, and VDR gene polymorphism in Korean labourers [10, 15, 17, 29]. The authors found that workers with Bsm I BB and Bb polymorphic marker genotypes had higher systolic and diastolic BP values and higher prevalence of AH compared with workers with bb genotype ($p<0.05$). In addition, workers with these genotypes had an earlier onset of AH and an increase in BP values with increasing age, compared with workers with bb genotype ($p<0.05$).

Urokinase plasminogen activator protein (UAP, also urokinase) is a human serineprotease encoded by the PLAU gene on chromosome 10. The protein owes its name to the fact that it was first isolated from human urine, but it has subsequently been found in various tissues and organs, including blood and extracellular matrix. UAP is a serine proteinase and a single-chain protein (mole mass 54 kDa) containing 411 amino acid residues. Limited proteolysis by plasmin or kallikrein hydrolyses the Lys-158-Ile-159 peptide bond to form a double-stranded enzyme. The N-terminal light chain of UAP, containing 158 residues, is linked to the heavy chain (253 amino acid residues) by a Cys-194-Cys-222 disulfide bond. The catalytic active centre of UAP is localised in the proteinase domain (residues 159–411) and includes His-204, Asp-255 and Ser-356. The N-terminal region contains a G-domain (residues 9–45) and one kringle (K, residues 45–134). Hydrolysis of the Lys-135-Lys-136 bond by plasmin results in the formation of low molecular weight double-stranded UAP. Low molecular weight single-chain UAP with a mole mass of 32 kDa is formed by hydrolysis of the Glu-143-Leu-144 peptide bond in a single-chain enzyme. Thrombin hydrolyses the Arg-156-Phe-157 peptide bond in the single-chain low molecular weight UAP, depriving the enzyme of activity in the resulting double-stranded protein. Enzymatic activity can be restored by plasmin hydrolysis of the Arg-158-Ile-159 peptide bond. In this case, a double-chain UAP with a molecular mass of 32 kDa is formed. In the UAP molecule, the carbohydrate component is attached to the Asn-302 residue.

The single-chain UAP directly activates plasminogen to plasmin, and then plasmin converts the single-chain UAP into a double-chain UAP, which activates plasminogen to plasmin. Although double-chain UAP shows no specificity against fibrin, its fibrinolytic activity is 2.5 times higher than the fibrinolytic activity of single-chain UAP. Thus, the conversion of single-chain UAP to double-chain UAP represents a positive feedback system that determines the rate of fibrinolysis under in vivo conditions.

The clinical manifestations of urolithiasis in children are highly variable. In uncomplicated cases (in 47 children), they are due to the passage of the nodule through the urinary tract, which is accompanied by mild or severe pain due to spasm and stone exit through the natural pathways. In the presence of larger stones in the urinary tract (27 children), the clinical symptomatology of nephroureterolithiasis was more often due to the accompanying pathology, i.e. calculous pyelonephritis or chronic renal insufficiency, rather than to the stones' obstruction of the calyx-lochanic system or their passage along the ureter. Pain (in 89 children) was the leading clinical manifestation of urolithiasis. They manifested themselves differently depending on age, nature and localisation of stones. Children of the first three years of life (31 children) responded to pain associated with spasms of the urinary organs in 80% of cases with general restlessness, crying, a rise in body temperature to 38 °C and above, sometimes dysuria and even macrohaematuria. At the age of 4 to 11 years (24 children) patients with urolithiasis complained of abdominal pain. This is due to the fact that at this age the kidneys are located lower than in older children and there is still no differentiated innervation of the urinary tract and abdominal organs. Hence the irradiation of pain mainly to the region of the abdomen, gastrointestinal disorders. Older children (41 children) localise pain in the lumbar region.

Dysuria in urolithiasis in children was significantly more frequent in early age (58%) and less frequent in older children (15%). The most common cause of dysuria is a combination of upper and lower urinary tract stones. Patients with low ureteral stones (17 children), especially in the juxtavesical and intramural sections, had pollakiuria, nicturia, and even acute urinary retention during renal colic. Dysuria in bladder stones (in 9 children) was due to irritation of the mucous membrane or acute cystitis.

Peculiarities of clinical course of urolithiasis in children. The clinical manifestations of urolithiasis in children are highly variable. In uncomplicated cases (in 47 children), they are due to the passage of the nodule through the urinary tract, which is accompanied by mild or severe pain due to spasm and stone exit through the natural pathways. In the presence of larger stones in the urinary tract (27 children), the clinical symptomatology of nephroureterolithiasis was more often due to the accompanying pathology, i.e. calculous pyelonephritis or chronic renal insufficiency, rather than to the stones' obstruction of the calyx-lochanic system or their passage along the ureter. Pain (in 89 children) was the leading clinical manifestation of urolithiasis. They manifested themselves differently depending on age, nature and localisation of stones. Children of the first three years of life (31 children) responded to pain associated with spasms of the urinary organs in 80% of cases with general restlessness, crying, a rise in body temperature to 38° C and above, sometimes dysuria and even macrohaematuria. At the age of 4 to 11 years (24 children) patients with urolithiasis complained of abdominal pain. This is due to the fact that at this age the kidneys are located lower than in older children and there is still no differentiated innervation of the urinary tract and abdominal organs. Hence the irradiation of pain mainly to the region of the abdomen, gastrointestinal disorders. Older children (41 children) localise pain in the lumbar region.

Dysuria in urolithiasis in children was significantly more frequent in early age (58%) and less frequent in older children (15%). The most common cause of dysuria is a combination of upper and lower urinary tract stones. Patients with low ureteral stones (17 children), especially in the juxtavesical and intramural sections, had pollakiuria, nicturia, and even acute urinary retention during renal colic. Dysuria in bladder stones (in 9 children) was due to irritation of the mucous membrane or acute cystitis.

Hyperthermic reaction as a manifestation of the general reaction of the organism to nephrolithiasis and its complications in children was observed quite often, and in children under 3 years of age it is manifested twice as often as in older children. Hyperthermic reaction indicates an active phase of the course of calculous pyelonephritis or pyonephrosis.

Syndrome of intoxication of the body can be considered the most characteristic manifestation of nephrolithiasis in childhood. Among young children, acute and chronic manifestations of intoxication were observed in 35%, and among children aged 3–15 years in 7% of cases. Acute intoxication is manifested by dry skin, decreased tissue turgor, anorexia. As a rule, there is a hyperthermic reaction with abnormalities of homeostasis parameters. Chronic intoxication leads to a decrease in body weight, anaemia, hypovitaminosis, decreased muscle tone, apathy.

Changes in urine in children with urolithiasis allow tentatively think about the pathology of the urinary tract. Haematuria in nephrolithiasis is an important diagnostic sign and was detected in 67% of patients. Microscopically it occurred in 85%. Pyuria, or leucocyturia, is also considered a symptom of urolithiasis, although it is more correct to consider it as a symptom of complications of calculous pyelonephritis, pyelonephrosis, cystitis, urethritis. Pyuria is detected in 95% of observations. Proteinuria is not characteristic of patients with nephrolithiasis.

Methods of treatment of urolithiasis depending on various factors of occurrence and course of urolithiasis. Methods of treatment of children with urolithiasis are diverse, but they can be divided into two main groups: conservative and operative. The choice of treatment method depends on the following factors: general condition of the patient, age, clinical course of the disease, size and localisation of the stone, anatomo-functional state of the kidney, stage of chronic renal failure. However, USD is primarily a surgical disease, so conservative therapy is not considered as an alternative to stone removal using one of the modern methods of surgical treatment. The only exception is concrements consisting of uric acid salts - urates, which can be successfully dissolved by citrate mixtures. Types of surgical treatment: open operations (pyelolithotomy, ureterolithotomy, etc.); remote shock wave lithotripsy (RWLT); percutaneous nephrolitholapaxy; transurethral endoscopic operations. The algorithm of treatment of patients with USD is as follows: in the presence of a stone in the middle and lower third of the pelvis, DLT and contact lithotripsy methods can be considered equivalent, especially if the size of the concrement is more than 2 cm. If the size of the stone does not exceed 2 cm, DLT should still be favoured. In nephrolithiasis of the upper third of the pelvis, contact lithotripsy is not optimal because the stones migrate downwards with the irrigation solution. If children with IBC have uric acid stones, it is better to try to dissolve them. With a competent approach to such treatment, its effectiveness is 47%, so all over the world in this case it is recommended to first carry out litholytic therapy, and only if it is ineffective, apply other methods. In turn, in coralloid nephrolithiasis, despite the presence of such promising treatment methods as DLT and contact lithotripsy, open surgery, including nephrectomy and kidney resection, is primarily indicated [1, 5, 6, 10, 29].

Conservative therapy of ICH includes: pharmacotherapy, diet therapy, detection and correction of metabolic disorders, anti-inflammatory therapy, effect on organ haemodynamics, immunomodulation. 'Stone expulsion' therapy is indicated for small uncomplicated ureteral nodules, which can move away independently, as well as after remote lithotripsy. As a rule, it includes antispasmodics, non-steroidal anti-inflammatory drugs, phytopreparations. The prescription of antibacterial drugs, taking into account the data of bacteriological examination of urine and endogenous creatinine clearance, is indicated in case of urinary tract infection [3, 4, 12, 14, 16, 28, 29].

Etiopathogenetic therapy may be aimed at the prevention of recurrence of stone formation and growth of the nodule, as well as dissolution of stones (litholysis). The diet of patients with USD provides: the use of sufficient fluid; depending on the metabolic disorders identified and the chemical composition of the stone is recommended to limit the intake of animal protein, table salt, products containing large amounts of calcium, purine bases, oxalic acid, a positive effect on the state of metabolism has a positive effect on the consumption of food rich in fibre. We can recommend some general principles in the observance of diet and water balance: maximum restriction of the total volume of food, its variety, limiting the consumption of food rich in stone-forming substances, fluid intake in the volume that maintains the daily amount of urine from 1.5 to 2.5 litres. Part of the liquid can be taken in the form of morsels of cranberries or cranberries, mineral water. Dietary therapy for calcium-oxalate stones consists of limiting the use of coffee and cocoa products (chocolate, etc.), strong tea, sorrel, spinach, lettuce, blackcurrants, strawberries, nuts, legumes, citrus fruits, cheese, cottage cheese, milk. At urate stones it is necessary to limit the intake of protein (animal origin) food, chocolate, coffee, alcohol, fried and spicy dishes and the exclusion of sub-products (pates, liver sausages, etc.), meat food in the evening. Phosphorus-calcium stones are excluded: alkaline mineral waters, milk, spices, spicy snacks, it is worth limiting the use of potatoes, beans, pumpkin, berries, green vegetables, cottage cheese, cheese, brynza. Recommended: meat food, grapes, green apples, pears, lard, flour products, vegetable fats, sauerkraut, cranberries, red currants, kefir, sour cream [5, 6, 7, 9, 13, 16, 30].

To date, open surgical interventions are allowed in some cases. This applies to complex situations (urinary tract reconstruction, purulent-inflammatory process, coral stones complicated by renal failure, etc.). The professionalism of urologists in performing this kind of kidney and ureter operations must be very high. No matter how fast the improvement and development of new minimally invasive methods of stone removal is carried out, it is impossible to solve the issues of urolithiasis treatment without a comprehensive interdisciplinary approach to postoperative treatment of children (consultation

of urologist, paediatrician, endocrinologist, nutritionist). After successful removal of the stone comes the extremely important stage of metaphylaxis of urolithiasis, which must necessarily include: treatment of concomitant diseases of the gastrointestinal tract, liver, endocrine glands, musculoskeletal system; active antibacterial therapy of urinary tract infection, carried out on the basis of urine culture studies (especially in children with phosphate nephrolithiasis); restoration of renal function; litholytic therapy (especially effective in urate nephrolithiasis) [2, 8, 30].

There are many methods to get rid of kidney and urinary tract stones. Until recently, this disease was treated mainly by open, often repeated and traumatic surgery, requiring a certain surgical experience and often accompanied by the development of complications. Treatment required a long stay in hospital and prolonged rehabilitation of patients [Dretler S.P. et al., 1995].

Currently, new surgical aids have been mastered and continue to be developed, allowing in most cases to avoid open surgery, and, without changing the fundamental principles and bases of treatment, to achieve the same result, but with significantly less risk to the organ and the patient. One of the promising techniques for the treatment of ureterolithiasis is contact lithotripsy, based on fragmentation of the nodule by its contact destruction [Sergienko N.F., Kuchits S.F., Shaplygin J1.B., et al., 2002].

There are several types of contact lithotripters: electrohydraulic, laser, ultrasonic, pneumatic. Their difference lies in the source and physical and mechanical parameters of the generated shock wave. 'The gold standard' of contact ureterolithotripsy regarding efficiency and safety is recognised as the method of pneumatic lithotripsy [Olefir Y.V., Avdeychuk Y.I., Akimenko M.Y. et al., 2004].

However, in the course of accumulating experience and analysing the long-term results of treatment of ureterolithiasis by contact destruction revealed that the frequency of intraoperative complications of traumatic and mechanical nature is quite high, especially in children. The total percentage of such complications reaches 10%. These include ballistic impact (3%), haematoma formation (3%), ureter perforation (1%), rupture (2%), wall rupture and complete ureter rupture (1%) [Marberger M., Fitzpatrick J.M., Jenkins A.D., et al., 1998; 2004]. According to the study of foreign colleagues, it was noted that the incidence of complications depends on the size of the nodule and the level of its localisation. Thus, with the size of the stone up to 5 mm, complications occur in isolated cases. The frequency of intraoperative complications increases significantly with increasing nodule diameter.

Endoscopic ureterolithotripsy, along with destruction of the nodule should provide minimal traumatic impact on the ureter wall. However, under the same conditions, the above complications still occur in a number of patients, the cause of which is poorly understood. Presumably, complications depend on the choice of lithotripter capacity, biomechanical properties of different levels of the ureter, stone strength and its chemical composition, as well as the state of the blood coagulation system and immune system. The biomechanical properties of the ureter depend on the patient's age group, the anatomical level of the ureter, and the genetically determined biomechanical properties of the patient's connective tissue [12, 17].

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