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Introduction. Crystalluria is a variant of the urinary syndrome, in which, according to the results of laboratory tests, an increased content of salt crystals is found in the urine. In the daily practice of a doctor this symptom is observed in almost every third child. The proportion of crystalluria in the structure of pediatric nephrological pathology exceeds 60% [1]. The most common is oxalate and oxalate-calcium crystalluria, which accounts for 71–75% [2,3]. Prolonged crystalluria leads to changes in the functional state of the kidneys or structural changes at the level of various parts of the nephron. The following phases of the pathological process are distinguished: preclinical (saline diathesis), clinical (dysmetabolic nephropathy, interstitial nephritis) and urolithiasis [4,5]. According to epidemiological studies, calcium oxalate nephropathies account for 14% of diseases of the urinary organs. Systems in children [6]. It has been established that intermittent calcium

HYPEROXALURIA AND CALCIUM OXALATE CRYSTALLURIA, DEVELOPMENT MECHANISMS AND CORRECTION POSSIBILITIES

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ABSTRACT

The article presents modern ideas of hyperoxaluria and oxalate-calcium crystalluria. Oxalic acid metabolism is investigated in normal and the main risk factors for hyperoxalaturia are considered. The clinical symptoms and diagnosis of hyperoxalaturia and oxalate-calcium crystalluria in children are described. Author presents basic principles of correction including diet therapy, drinking regime, phytotherapy, medication

oxalate crystalluria, detected in childhood and adolescence, leads to the progression of tubulointerstitial disorders in adults and an increase in the frequency of a mixed variant of the urinary syndrome, characterized by severe proteinuria, hematuria, signs of membranolytic of the tubular epithelium of the kidneys, functional and structural changes in the kidneys and bladder [7].

Oxalate metabolism and mechanisms of development of hyperoxaluria, oxalate-calcium crystalluria. According to modern concepts, the homeostasis of oxalic acid in the body is maintained by two exogenous sources (food and ascorbic acid) and endogenous - the metabolism of amino acids glycine and serine. Normally, oxalates found in foods bind to calcium in the intestinal lumen and are excreted from the body mainly with feces in the form of insoluble calcium oxalate. The usual diet contains 0.1-1.0 g of oxalates, but only 2-5% of them are absorbed in the intestines.



Most of the oxalates excreted in the urine are formed in the process of metabolism from amino acids - serine, glycine, hydroxyproline, and partly from ascorbic acid [8]. Under physiological conditions, 10% of the oxalates excreted in the urine are formed from ascorbic acid and 40% from glycine.

Excess oxalates are excreted mainly by the kidneys. Supersaturation of urine with oxalates eventually leads to their precipitation in the form of crystals. Normally, urine is a supersaturated saline solution, which is in a state of dynamic equilibrium due to substances (inhibitors) that contribute to the dissolution or dispersion of its constituents.

A decrease in the activity of inhibitors increases the risk of hyperoxaluria (Tamma-Horsfall, osteopontin, bikunin and prothrombin fragment 1) [9]. The high affinity of oxalate for calcium and the low solubility of calcium oxalate have been proven. Urinary oxalate is the only strong chemical promoter of kidney stone formation, about 15 to 20 times more potent than excess urinary calcium.

In the metabolism of oxalic acid, magnesium plays an important role, which affects the release of oxalic acid, increases the solubility of calcium phosphate, and also prevents the crystallization of oxalates [10].

There are two etiopathogenetic variants of hyperoxaluria - primary and secondary. Primary hyperoxaluria is a hereditary disease that includes three rare types of genetically determined disorders of glyoxylic acid metabolism, which are characterized by increased excretion of oxalates, recurrent calcium oxalate urolithiasis and/or nephrocalcinosis, and a progressive decrease in glomerular

filtration rate with the development of chronic renal failure [11,12]. In pediatric practice, secondary or spontaneous hyperoxaluria is most common, which can be transient (with a monotonous diet, against the background of acute respiratory viral infections, intercurrent diseases) or permanent. There are several mechanisms of its development. Alimentary hyperoxaluria is associated with excessive consumption of products containing oxalic and ascorbic acids [13]. The intestinal form of hyperoxaluria is due to increased absorption of oxalates and is observed in chronic inflammatory bowel diseases, food allergies. In addition, an increase in the absorption of oxalates is noted in all conditions accompanied by impaired absorption of fats in the intestine (cystic fibrosis, pancreatic insufficiency, short bowel syndrome). Most fatty acids are absorbed in the proximal intestine. Decreased absorption of fatty acids results in calcium loss as the latter binds to them. This leaves insufficient free calcium available for oxalate binding in the distal lower intestine, resulting in a dramatic increase in oxalate resorption and urinary excretion [14]. There are a number of other factors that favor intestinal hyperoxaluria, namely: decreased diuresis associated with diarrhea; a decrease in the excretion of magnesium ions by the kidney due to a decrease in their absorption in the intestine; metabolic acidosis due to the loss of bicarbonates in the intestine. A significant role in the genesis of intestinal hyperoxaluria is played by intestinal dysbacteriosis, which results in a decrease in the number of colonies of bacteria *Oxalobacter formigenes*, which break down about 50% of exogenous oxalate. The absence or reduction of *Oxalobacter*



formigenes in the intestine increases the availability of oxalate for absorption and increases its concentration in the blood and urine [15]. For the development of hyperoxaluria, a decrease in urinary excretion of citrates (an inhibitor of oxalate crystallization), vitamin B6 deficiency (an inhibitor of oxalate formation) is also important [16].

Risk factors for secondary hyperoxaluria include hereditary predisposition, which is observed in 71% of cases in children with hyperoxaluria. This is manifested not only by the pathology of oxalate metabolism, but also by a tendency to instability of cytomembranes [17]. In the genesis of membrane destabilizing processes, an important role belongs to the processes of intensification of lipid peroxidation, activation of endogenous phospholipases and oxidative metabolism of granulocytes. With the destruction of acidic phospholipids of cell membranes, oxalate precursors are formed. Local formation of oxalates in the kidneys is possible. The causes of membrane breakdown in this case are bacterial phospholipases in pyelonephritis, exposure to membrane toxic compounds, such as sulfa drugs, environmental factors, etc., as well as seasonal climatic fluctuations, nutritional errors, emotional and physical stress.

The connection of hyperoxaluria with undifferentiated connective tissue dysplasia was noted, since oxalates are the end product of the metabolism of glycine, serine, hydroxyproline, which are included in composition of collagen [18].

Clinical manifestations. The first manifestations of hyperoxaluria in children can be already in the first year of life. Most often, hyperoxaluria is recorded during periods of intensive growth of a child 7-8

and 10-14 years old. In most cases, oxalate crystalluria is detected by chance, sometimes against the background of acute respiratory viral infections, intercurrent diseases. Often, parents notice in a child a decrease in the volume of urine during the day, the precipitation of a large amount of salts. When questioned in children, recurrent abdominal pain is detected. Sometimes inflammation of the genitals develops due to constant irritation of the skin and mucous membranes, while urinating, there may be a burning sensation or other dysuric disorders. Against the background of crystalluria, an infection of the urinary system is often formed.

A visual assessment of urine indicates its saturated character, spontaneous sedimentation is possible. Hyperstenuria (urine relative gravity greater than 1030) in the absence of glucosuria should alert for hyperoxaluria.

In the future, against the background of crystalluria, slight microhematuria and / or proteinuria, abacterial leukocyturia appear, which indicates damage to the kidneys and is referred to as "dysmetabolic nephropathy".

Diagnostics. Microscopic examination of the urinary sediment can reveal oxalate colorless crystals in the form of postal envelopes, which is not the basis for the diagnosis of hyperoxaluria. Biochemical study of daily urine (transport of salts) allows you to clarify the presence of hyperoxaluria and hypercalciuria. The normal level of oxalates is less than 0.57 mg/kg/day, calcium is less than 4 mg/kg/day. [19]. In children with hyperoxaluria in nephrological hospitals, an analysis is carried out for the anti-crystal-forming ability of urine to calcium



oxalate, which is reduced. The test for peroxide in the urine allows you to evaluate the activity of the processes of lipid peroxidation of cytomembranes.

An ultrasound examination of the kidneys in some children reveals echopositive inclusions in the pelvis and calyces.

Treatment. Basic therapy for hyperoxaluria and calcium oxalate crystalluria includes therapeutic nutrition and sufficient drinking regimen [21]. The main dietary recommendations are the creation of a rational balanced diet, taking into account the age needs of the child and the characteristics of impaired metabolism. With hyperoxaluria, foods with a high content of oxalic acid (1.0-10.0 g / kg of product weight) are excluded - chocolate, cocoa, tea, sorrel, spinach, parsley, beets, rhubarb, beans, nuts, buckwheat. Foods containing a moderate amount of oxalates (0.3-1.0 g / kg of product weight) are limited - black currants, sour varieties of apples and berries, beans, carrots, tomatoes, citrus fruits, as well as rich in vitamin C - rose hips, peppers sweet, sea buckthorn, cauliflower.

With hypercalciuria, the appointment of a diet low in sodium is indicated. To do this, it is enough to exclude salted crackers, chips, pasta, processed cheese, sausage, canned vegetable juices, tomato sauce, pickles. The use of calcium with food and drinks should correspond to the age requirement: for children 1-3 years old - 500 mg / day, 4-8 years old - 800 mg / day, 9 years and older - 1300 mg / day. The average calcium content in foods is as follows: milk (240 ml) - calcium 300 mg, cottage cheese (113 g) - 110 mg, yogurt (170 g) - 250 mg, cheese (28 g) - 195-335 mg, ice cream (113 d) - 100 mg. Sufficient drinking regimen is a universal way to

treat any crystalluria, as it helps to reduce the degree of saturation of salts in the urine.

The daily fluid requirement is at least 50 ml/kg. It is recommended to take weakly alkaline and low-mineralized mineral waters in the amount of 3-5 ml/kg/day. in three doses, a course of one month, 2-3 times a year. The basis of drug treatment is antioxidant and membrane stabilizing therapy, since one of the links in the pathogenesis of hyperoxaluria in most cases is membranopathy [22]. Within 3-4 weeks, vitamin A should be prescribed quarterly (1000 IU / year of the child's life per day), vitamin E (1-1.5 mg / kg of body weight per day, not more than 15 mg / day).

An obligatory component of the therapy of hyperoxaluria and calcium oxalate crystalluria is the use of phytopreparations. Despite the large selection of medicinal plants and their preparations, it is important to use only those whose effectiveness and safety have been proven by scientific research. Such a phytopreparation is Uralesan, standardized according to the content of biologically active substances of medicinal plants: active substances in 100 ml: fir oil - 0.419 g, peppermint oil - 0.105 g, liquid extract of wild carrot fruits - 1.204 g, liquid extract of hop cones - 1.726 g, oregano herb liquid extract - 1.195 mg. those. high-quality natural remedy with fully studied and proven properties of plants, strict observance of the principles of selection and careful selection of seed material, cultivation of raw materials on plantations in an ecologically safe area, standardization of each stage of production, litholytic, membrane-stabilizing and antioxidant effects. The drug "Uralesan" also helps to



maintain the pH of urine in the range of 6.2-6.8, binds calcium into chelate complexes [23]. In an experimental and clinical study, the ability of the components of the phytopreparation Uralesan to suppress the processes of pathological crystallization of urine in urolithiasis in 86% of cases after 20 days of its administration was proved.

Metabolic therapy includes the use of magnesium preparations, vitamin B6. The preferred form of magnesium in this case is magnesium citrate, as this substance is an inhibitor of the crystallization of oxalates in the urine. The drug, which includes magnesium citrate (100 mg Mg++) and vitamin B6 (10.0 mg), is called "Magne-B6 Antistress" (children over 6 years old 10-30 mg / kg / day). expedient it the appointment of a course for two months three times a year. Children with hypercalciuria are contraindicated in calcium and vitamin D preparations, with hyperoxaluria - ascorbic acid preparations. Another such effective phytopreparation is Canephron N (Bionorica SE, Germany), standardized by the content of biologically active substances of medicinal plants: centaury herb (Centaurii herba), lovage root (Levistici radix), rosemary leaves (Rosmarini folia). This is a phytonearing preparation, i.e. high-quality natural remedy with fully studied and proven properties of plants, strict adherence to the principles of selection and careful selection of seed material, growing raw materials on plantations in an ecologically safe area, standardization of each stage of production Pharmacological properties of the drug "Canephron N", except for anti-inflammatory, antibacterial, antispasmodic - have diuretic, litholytic, membrane-stabilizing and antioxidant effects. The

drug "Canephron N" also helps to maintain the pH of urine in the range of 6.2-6.8, binds calcium into chelate complexes [23]. V.V. Length et al. [26] studied the clinical efficacy of Canephron N for 3 months in children with sporadic dysmetabolic nephropathy with calcium oxalate crystalluria. It was shown that treatment with Canephron N compared with therapy with a complex of vitamins (A, E, B6-2 courses for 3 weeks with a break of 6 weeks) is more effective and leads to a faster and more significant decrease in the frequency and severity of hematuria, hyperoxaluria, calciuria and lipiduria. The results also showed that the most the effectiveness of therapy is achieved only by three months of treatment with Canephron N. In many articles it is written that the use preparations "Uralesan" and "Kanefron N" for six months (14 days a month) against the background of complex treatment of children with impaired oxalate metabolism provided a significant decrease in the level of daily excretion of oxalates [27]. Membrane stabilizing properties of the drug "Canephron N" are shown in the study by K.E. Kazakova et al. [28]. The use of the drug for one month as monotherapy or in combination with vitamins A, E, Essentiale in children with dysmetabolic nephropathy (oxalaturia - in 75%) led to the elimination of hyperoxaluria, the normalization of lipid peroxidation processes in the cell and, consequently, to the stabilization of cell membranes. Thus, the preparations "Uralesan" and "Canephron" can be used both in a medical complex and separately for a long course in children with hyperoxaluria and calcium oxalate crystalluria. With intestinal hyperoxaluria, depending on its causative factor, therapy



is expanded by the inclusion of probiotics, enzymes, and calcium preparations.

In conclusion, it should be emphasized that early detection of oxalic acid metabolism

disorders and their timely correction can prevent the development of metabolic (oxalate or calcium oxalate) nephropathy in children.

References:

1. Averyanova N.I., Balueva L.G. Oxalate crystalluria in children. *International Journal of Applied and Basic Research* 2012; 5:25-27.
2. Averyanova N.I., Balueva L.G., Ivanova N.V., Rudavina T.I. Violation of the metabolism of oxalic acid in children. *Electronic scientific journal: Modern problems of science and education* 2015;3.
3. Bagdasarova I.V., Stoeva T.V., Zheltovskaya N.I. The study of clinical and laboratory features in dysmetabolic nephropathies in children. *Perinatology and pediatrics*, 2009; 3(39):71-73.
4. Voronina N.V., Gribovskaya N.V., Evseev A.N., Ezersky D.V. Peculiarities of urinary syndrome in patients with oxalate nephropathy in comparison with nephrobiopsy results. *Far Eastern Medical Journal* 2013;3:15-20.
5. Gavrilova V.A., Malkoch A.V. Dysmetabolic nephropathy. *Attending physician* 2006; 1:32-36.
6. Gordeeva E.A., Vrzhesinskaya O.A., Kodentsova V.M., Kharitonchik L.A., Alekseeva N.V., Dunaeva I.P. Pathogenetic role of vitamin B2 and B6 deficiency in the development of dysmetabolic nephropathies in children. *Questions of modern pediatrics* 2004; 6(3):32-34.
7. Gres A.A., Voshchula V.I., Rybina I.L., Shloma L.P. Urolithiasis: experience with the use and effectiveness of Kanefron. *Medical News* 2004;
8. Dlin V.V., Shatokhina O.V., Osmanov I.M., Yurieva E.A. Efficiency of Kanefron® N in children with dysmetabolic nephropathy with oxalate-calcium crystalluria. *Bulletin of Pediatric Pharmacology and Nutrition* 2008; 4(5):66-69.
9. Dlin V.V., Ignatova M.S., Morozov S.L., Yurieva E.A., Osmanov I.M. Dysmetabolic nephropathy in children. *Russian Bulletin of Perinatology and Pediatrics* 2012; 5(57):36-44.
10. Dlin V.V., Osmanov I.M. Dysmetabolic nephropathy with oxalate-calcium crystalluria. *Effective pharmacotherapy* 2013; 42:8-26
11. Zverev Ya.F., Zharikov A.Yu., Bryukhanov V.M., Lampatov V.V. Modulators of oxalate nephrolithiasis. crystallization inhibitors. *Nephrology* 2010; 1(14):29-49.
12. Zubarenko A.V., Stoeva T.V. Dysmetabolic nephropathy in pediatric practice. *Message 1. Principles of diagnostics. Health child* 2009; 4(19):132-136.
13. Zubarenko A.V., Stoeva T.V. Dysmetabolic nephropathy in pediatric practice. *International Journal of Pediatrics, Obstetrics and Gynecology Traven/Cherven* 2016 Volume 9 No. 3 Message 2. Principles of treatment and prevention. *Child Health* 2011; 3(30):97-104.
14. Ignatova O.A., Markova V.I., Menshikova L.I., Tyukova N.V. Connective tissue dysplasia in children with oxalate nephropathies. *Ros.pediatric journal* 2003; 6:29-31.
15. Kazakova K.E., Kondratieva E.I., Terent'eva A.A., Sukhanova G.A. Experience in the rehabilitation of children with dysmetabolic nephropathies living in an industrial city. *Questions of modern pediatrics* 2009; 1(8):41-45.



16. Guidelines on Urolithiasis European (EAU, 2013) (abridged) Association of Urology 2013/ Kidney Journal 2013; 4(06):44-54.
 17. Rychkova S.V. .Dysmetabolic nephropathy in pediatric practice. Attending Physician 2010;8:11-15.
 18. Smirnova I.S., Ignatova O.A. Risk factors for the development of secondary oxaluria in children. Literature review. Human Ecology 2009; 11:57-62.
 19. Sukalo A.V., Shevchenko O.S. The use of Canephron N in dysmetabolic nephropathies in children. Recipe: scientific and practical magazine for pharmacists and doctors 2009; 1(63):106-110.
 20. Battino B.S., DeFoor W., Coe F., Tackett L., Erhard M., Wacksman J. et al. Metabolic evaluation of children with urolithiasis: are adult references for supersaturation appropriate? J Urol. 2002;168:2568–71.
 21. Gambardella R., Richardson R. The pathmays of oxalate formation from phenylalanine, tryptophan and ascorbic acid in the rat. Biochim. Biophys. Acta 1977; 499:156–168.
 22. Kaufman D.W., Kelly J.P. , Curhan G.C., Anderson T.E. , Dretler S.P., Preminger G.M. et al. Oxalobacter formigenes May Reduce the Risk of Calcium Oxalate Kidney Stones. J Am Soc Nephrol. 2008 Jun; 19(6):1197–1203.
 23. Lyon E.S., Borden T.A., Ellis J.E., Vermeulen C.W. Calcium oxalate lithiasis produced by pyridoxine deficiency and inhibition with high magnesium diets. Invest Urol. 1966 Sep; 4(2):133-142.
 24. Massey L.K., Liebman M., Kynast-Gales S.A. Ascorbate increases human oxaluria and kidney stone risk. J Nutr. 2005 Jul;135(7):1673-1677.
 25. Naber K.G. Efficacy and safety of the phytotherapeutic drug Canephron® N in prevention and treatment of urogenital and gestational disease: review of clinical experience in Eastern Europe and Central Asia. Res Rep Urol.2013 Feb4;5:39-46.
 26. Nicoletta J., Lande M. Medical evaluation and treatment of urolithiasis. Pediatr Clin North Am 2006; 53:479-491.
- Williams H.E. Oxalic acid and the hyperoxaluric syndromes. Kidney Intern. 1978; 13:410-417.