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Dysmetabolic Nephropathies in Children

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Abstract: The paper gives the present views of sporadic dysmetabolic nephropathy: its pathogenesis, diagnostic methods, morphology, clinical features, treatment, and prevention. It shows current treatment modalities for dysmetabolic nephropathy with calcium oxalate crystalluria and presents data on medicaments recommended for use in children, as well as dietary therapeutic features.

Keywords: children, sporadic dysmetabolic nephropathy, calcium oxalate crystalluria, medications, dietary therapy.

The problem of sporadic dysmetabolic nephropathies is very relevant in pediatrics and pediatric nephrology. This is due to the high frequency of pathology in the population, as well as the possibility of its progression up to the development of urolithiasis and/or interstitial nephritis. An effective solution to this problem is possible by combining the achievements of normal and pathological physiology, clinical medicine, pathological anatomy, biochemistry, pharmacology, immunology and nephrology. The use of such a complex of knowledge of modern medicine is determined by the need to study the complex processes that determine the role of the kidneys in maintaining, together with intestinal enterocytes and other systems, the constancy of the internal environment of the body, as well as the importance of these processes in the regulation of blood circulation and hematopoiesis, carbohydrate and lipid metabolism. This ensures autoregulation of the operating mode of both the kidneys themselves and the body as a whole.

Terminology. Dysmetabolic nephropathies are understood as a large group of nephropathies with different etiologies and pathogenesis, developing as a result of metabolic disorders. Metabolic pathology leads to changes in the functional state of the kidneys or to structural changes at the level of various elements of the nephron.

Dysmetabolic nephropathies in the broad sense of the word combine diseases associated with severe disorders of water-salt metabolism that develop in gastrointestinal diseases with toxic syndrome and hemodynamic disorders. These may include kidney damage that occurs against the background of defects in phosphorus-calcium metabolism in hyperparathyroidism, hypervitaminosis D and other diseases.

The term “dismetabolic nephropathy” can also be used in a narrower sense to designate polygenically inherited (multifactorially developing) nephropathy, which is associated with the pathology of oxalic acid metabolism and manifests itself in conditions of familial instability of cytomembranes [1]. Clinically, it is dysmetabolic nephropathy with calcium oxalate crystalluria, which covers various variants of the disease: secondary tubulopathy with minimal clinical and morphological manifestations, interstitial nephritis developing as a result of impaired oxalate metabolism, and urolithiasis. In its pathogenetic essence, dismetabolic nephropathy with calcium oxalate crystalluria is a variant of renal membranopathy. In recent years, it has been established that the so-called secondary oxalate nephropathy, in contrast to primary hyperoxaluria caused by

impaired metabolism of glyoxylic acid, includes a heterogeneous group of polygenically inherited kidney diseases associated with the pathology of oxalic acid metabolism and developing in conditions of instability of cell membranes [1, 2]. In this case, in the genesis of membrane-destabilizing processes in tissues, an important role belongs to the intensification of lipid peroxidation, activation of endogenous phospholipases, and reactions of oxidative metabolism of granulocytes [3].

Pathogenesis. Pathogenetically, this is a heterogeneous group of diseases, and the development of dysmetabolic nephropathy with calcium oxalate crystalluria may be due to the following factors [1]:

- increased synthesis of glyoxylate from glycine and proline under conditions of oxidative stress, activation of monoamine oxidases in the presence of defects in local antioxidant defense (oxidative hypothesis);
- insufficiency of membrane mechanisms for protecting cells from calcium ions - inferiority of the calcium-magnesium ATPase system, etc. (calcium hypothesis);
- partial deficiency of the enzyme alanine-glyoxylate transaminase (hypothesis of polygenic variations in the metabolism of glyoxylic acid);
- activation of phospholipases and accelerated metabolism of membrane phospholipids: phosphatidylserine and phosphatidylethanolamine as sources of serine and ethanolamine, metabolized through glycolate-glyoxylate into oxalic acid (hypothesis of cytomembrane instability);
- deficiency or destruction of biological and chemical stabilizers of oxalic acid and calcium ions (hypothesis of deficiency of oxalate formation inhibitors);
- increased crystallization of calcium oxalate under conditions of increased concentration of uric acid in the blood and urine (epitaxy hypothesis).

Most of the oxalates excreted in the urine are formed during metabolism from amino acids - serine, glycine, hydroxyproline, partly from ascorbic acid; a small amount comes from the intestines when oxalogenic foods are taken with food (carrots, spinach, tomatoes, chocolate, coffee, etc.). An increase in the synthesis of oxalates (except for hereditary metabolic defects) may be associated with excessive formation of their precursors in the body, pyridoxine deficiency, and ethylene glycol poisoning. Excessive synthesis of oxalates is also observed with gout and after intestinal surgery (ileostomy). In recent years, attention has been drawn to the possibility of local formation of oxalates in the kidneys, which is associated with the destruction of phospholipids of cell membranes, resulting in the accumulation of oxalate precursors (serine), as well as phosphates, with which calcium forms insoluble salts.

The immediate causes of the breakdown of membrane phospholipids are renal ischemia, activation of endogenous or the appearance of bacterial phospholipases, exposure to membrane-toxic compounds and, possibly, the formation of toxic forms of oxygen (oxygen with an unpaired electron, superoxide anion, hydroxyl radical). The instability of cell membrane structures is inherited as a polygenic trait.

Various contributions of genetic and environmental factors to the formation of oxalate nephropathy have been established. The linkage of signs of oxalate diathesis and oxalate nephropathy with tissue antigens of the 1st class was revealed, as evidenced by a significant predominance of the B7 phenotype in these children and a less reliable A28. Inheritance of oxalate diathesis and oxalate nephropathy corresponds to the polygenic inheritance model, the heritability coefficient is 40 and 46%, respectively [4].

Morphology. Morphological examination reveals destruction of the proximal brush borders and changes in the distal tubules. In the case of the development of interstitial inflammation in children with dysmetabolic nephropathy with calcium oxalate crystalluria, pronounced

lymphohistiocytic infiltration of the interstitium, phenomena of focal sclerosis, and sometimes a mesangioproliferative reaction of glomeruli are noted. Calcium oxalate crystals are often found in the lumen of the tubules and interstitium [1]. In Fig. Figures 1 and 2 (kindly provided by Prof. A.I. Klembovsky) show morphological changes characteristic of dysmetabolic nephropathy with calcium oxalate crystalluria.

Clinical manifestations. The first signs of dysmetabolic nephropathy with calcium oxalate crystalluria are often detected accidentally at the age of 3-4 years. Clinically, the disease is mild and manifests itself with minor signs of intoxication, arterial hypotension in 50% of cases, as well as symptoms of vegetative-vascular dystonia - frequent headache, lability of pulse and blood pressure. In some cases, symptoms are observed that indicate an interest in the hypothalamic-diencephalic region, in the form of excess body weight (+2 sigma deviations), sweating and decreased diuresis in the absence of edema. Often, attention is paid to a decrease in the volume of urine during the day and its rich character.

Dysmetabolic nephropathy with calcium oxalate crystalluria is characterized by mixed urinary syndrome with the presence of hematuria of varying severity in combination with proteinuria, most often microproteinuria. Leukocyturia in this variant of nephropathy is abacterial, predominantly mononuclear in nature. The presence of oxalate crystals in the urine is mandatory, most often in the form of large and/or small aggregates. All patients have signs of cytomembrane instability, which are manifested not only by calcium oxalate crystalluria, but also by hyperoxaluria, increased urinary excretion of ethanolamine and lipids. A characteristic decrease in the anti-crystal-forming ability of urine is associated with a decrease in the amount of natural stabilizers in the urine (pyrophosphates, polyphosphates, ATP, etc.)

Almost all children with preserved glomerular filtration have nocturia, and even with normal diuresis, hypersthenuria (up to 1030 and above) in the absence of glucosuria. The progression of dysmetabolic nephropathy with calcium oxalate crystalluria can lead to the formation of abacterial tubulointerstitial nephritis, as well as be complicated by an infection of the urinary system [5].

Secondary hyperoxaluria (regardless of the stage of the clinical continuum) is characterized by hyperoxaluria and/or calcium oxalate crystalluria (large aggregated crystals more than 12 microns) with a decrease in the anti-crystal-forming ability of urine, increased excretion of lipids, ethanolamine, phosphoethanolamine. Secondary hyperoxaluria associated with polygenically inherited membranopathy is characterized by the presence of a similar pattern in several family members [1,5].

Oxalate diathesis is a common condition in children. Population studies of children in a non-endemic region for urolithiasis conducted at the end of the twentieth century using selective screening using spontaneous crystalluria and crystallometry established a high frequency of oxalate diathesis - 160:1000. The prevalence of oxalate nephropathy was significantly lower, 31.7 per 1000 children [4].

Oxalate diathesis is diagnosed in the case of the above laboratory symptoms in the absence of urinary syndrome and renal dysfunction. Dysmetabolic nephropathy with calcium oxalate crystalluria is characterized by the appearance of urinary syndrome in the form of minimal hematuria, proteinuria and/or abacterial leukocyturia. There is a correlation between the size of the crystals, their aggregation and the severity of clinical manifestations of oxalate nephropathy; There is no correlation between the amount of oxalic acid excretion and the development of oxalate nephropathy.

It is often difficult to draw the line between dysmetabolic nephropathy with calcium oxalate crystalluria and tubulointerstitial nephritis of metabolic origin, since with the latter, a decrease in tubular kidney function occurs only at a fairly late stage of the disease. The basis for diagnosis may be the severity of urinary syndrome and, above all, hematuria and proteinuria. The development of the interstitial process is confirmed by the detection of increased excretion of

enzymes in the urine (alkaline phosphatase, gamma-glutamyltransferase, lactate dehydrogenase, etc.), microalbuminuria and microglobulinuria (α1 - and β2 -microglobulin), and when determining the selectivity of proteinuria, a tubular type of proteinogram is characteristic.

The development of the tubulointerstitial process in children with dysmetabolic nephropathy with calcium oxalate crystalluria can occur in two directions. The first direction is the development of an abacterial inflammatory tubulointerstitial process due to the effect of calcium oxalate crystals (and others) on the activation of the complement system along the alternative pathway, which leads to the release of proinflammatory cytokines and activation of the Hageman factor. In addition, the possibility of the formation of toxic forms of oxygen by leukocytes under the influence of calcium oxalate crystals was established in vitro. The second way is the development of a bacterial tubulointerstitial process in patients with dysmetabolic nephropathy with calcium oxalate crystalluria. In this case, the activation of phospholipases A and C is important. Often these two processes are combined.

The maximum severity of dysmetabolic disorders can cause the occurrence of urolithiasis, even in the first years of life. In other cases, the disease is more often detected "by chance."

In regions where there is long-term exposure of children to heavy metals, phenocopies of dysmetabolic nephropathy with calcium oxalate crystalluria are detected, which are clinically indistinguishable: hematuria, calcium oxalate crystalluria and/or hyperoxaluria are observed. Kidney damage due to chronic exposure to heavy metals (cadmium, chromium and some others) is due to the long half-life of these elements from the body and their ability to form a depot in the renal cortex [6], i.e., in essence, these are toxic nephropathies. Studies conducted in a number of regions with elevated levels of heavy metals and, above all, cadmium, have shown that only with careful examination can differences between these conditions be identified.

Econephropathy associated with chronic exposure to heavy metals (cadmium, chromium) is characterized by the following symptoms [7]:

- latent microhematuria with calcium oxalate crystalluria and/or hyperoxaluria;
- violation of the stability of tubular cytomembranes;
- decreased function of the proximal tubules of the kidneys in the early stages of the disease;
- combined functional disorders of the kidneys in later stages of the disease.

It has been established that econephropathy is a multifactorial disease in which the share of environmental factors in development (according to the model of Edwards J., 1969) prevails over hereditary ones (53 versus 47%) [8]. In dysmetabolic nephropathy, the significance of hereditary factors is higher than in econephropathies (55 versus 45%).

Treatment. The basis of the treatment of dysmetabolic nephropathy with calcium oxalate crystalluria is the regular use of a therapeutic diet, which is a rational mixed diet that eliminates the functional load for the active part of the nephron - the tubular apparatus. The diet is called the potato-cabbage diet, as it consists mainly of potatoes, cabbage and other vegetables prepared in various ways. The exclusion of extractive broths and oxalogenic products, including leafy vegetables, strong tea, and cocoa is provided. White bread, fresh lard, vegetable and butter, and sour cream are allowed. In order to "alkalize" the body and prevent hypokalemia and hypomagnesemia, a large amount of unsweetened fruits (pears, prunes, dried apricots) is introduced.

Taking into account the growing needs of the child's body for animal protein, meat is not limited to the diet, but is recommended only in boiled form and in the first half of the day. The ratio of main ingredients (proteins, fats, carbohydrates) in food is maintained within the limits of age requirements.

Children with dysmetabolic nephropathy with calcium oxalate crystalluria are prohibited from foods high in vitamin C and oxalic acid: peas, beans, beans, beets, radishes, radishes, lettuce,

sorrel, spinach, parsley, dill, rose hips, currants, citrus fruits; as well as calcium-containing products: cheese, cottage cheese, cocoa, strong broths, canned meat and fish. Allowed in limited quantities: cereals, flour, pasta, butter, milk, liquid dairy products, eggs, pasta, tomatoes, boiled meat and fish, boiled sausages, onions, corn.

Allowed: bananas, apples (except Antonovka), pears, dogwoods, plums, quinces, peaches, apricots, strawberries, strawberries, all melons, potatoes, white cabbage, cucumbers, cranberry juice.

The use of a potato-cabbage diet for 2-3 weeks is accompanied by a statistically significant decrease in oxalate excretion, which is combined with an improvement in urinary syndrome. The potato-cabbage diet is prescribed for 3 weeks with 3-week breaks, when the child receives diet No. 5 according to Pevzner.

A typical diet contains from 97 to 930 mg of oxalates, but only 2.3-4.5% of them are normally adsorbed in the intestines. Under physiological conditions, 10% of oxalates excreted in urine are formed from ascorbic acid and 40% from glycine.

Potatoes contain a moderate amount of oxalic acid, which is almost not absorbed from the gastrointestinal tract, since this product contains significant amounts of calcium, which keeps oxalates in an undissolved state and ensures their almost complete excretion in feces. Animal products are generally low in oxalic acid. However, significant amounts of it are contained in connective tissue: tendons, cartilage, rich in collagen, and, therefore, the closest precursors of oxalates are the amino acids hydroxyproline and glycine.

To increase diuresis, a large amount of fluid is prescribed (2 liters per 1.73 m2 of body surface). It is very important to maintain a high-fluid regime at night, when the urine is more concentrated, which creates conditions for salt crystallization. The use of agents that stabilize cell membranes is indicated: antioxidants, dimephosphone, xydiphone, potassium and magnesium salts, repeated courses of vitamins B6, A, E.

The membrane-stabilizing effect of vitamin B6 (pyridoxal phosphate) is due to its participation in fat metabolism as an antioxidant, as well as in the metabolism of amino acids, potentiating their decarboxylation and transamination. Prescribed at a dose of 1-3 mg/kg per day in the first half of the day for 3-4 weeks quarterly.

The membrane-stabilizing effect of vitamin A is due to the ability to integrate into the lipid layer and participate in the interaction of proteins and lipids in the membrane. Prescribed at a dose of 1000 units per year of life per day for 3-4 weeks quarterly.

Vitamin E (tocopherol acetate) is a natural antioxidant responsible for protein-lipid bonds in membranes and other important processes of cellular metabolism. Prescribed together with vitamin A at a dose of 1-1.5 mg/kg per day, but not more than 15 mg per day in courses of 3 weeks per quarter. The use of vitamin E is limited in children during puberty.

For membrane stabilizing purposes, dimephosphone is prescribed, a domestic membrane-stabilizing drug that can restore respiratory phosphorylation in mitochondrial membranes, which leads to a decrease in lipid peroxidation processes. Available in the form of a 15% solution. The dosage is 1 ml for every 5 kg of body weight or 30 mg/kg in 3 divided doses over 2-4 weeks, 3 courses per year.

In children with dysmetabolic nephropathy with calcium oxalate crystalluria, magnesium preparations are used with caution, since their overdose may cause the development of magnesium salts in the urinary tract. The rationale for using magnesium supplements is that it serves as a natural physiological antagonist of calcium and prevents its accumulation in tissues and fluids. Magnesium preparations include magnesium oxide (under 7 years of age - 100 mg in 2 doses, from 7 to 10 years - 150 mg in 3 doses, over 10 years - 200 mg in 2 doses) for 3-4 weeks quarterly. It is optimal to use the drug Magnerot as a magnesium donor, which contains

magnesium orotate dihydrate (500 mg in 1 tablet, 32.8 mg of magnesium). Magnerot contains orotic acid, which promotes cell growth and participates in the metabolic process. In addition, orotic acid is necessary for the fixation of magnesium on ATP in the cell and the manifestation of its action. The drug is taken 1-2 tablets 3 times a day for 7 days, then at half the dose for another 3 weeks, with a small amount of liquid.

In children with dysmetabolic nephropathy with calcium oxalate crystalluria, herbal remedies and medicinal plants that have litholytic properties, improve metabolic processes, promote the excretion of metabolic products not only through the urinary system, but also through the gastrointestinal tract, and also have an antioxidant effect are widely used in therapy. (especially those containing flavonoids). Herbal medicine should be carried out regularly using herbal collections (including no more than three) for 1 month quarterly: knotweed, dill, golden rod, wild strawberry, horsetail, peppermint, wheatgrass, corn silk.

Among the combined herbal preparations, it is recommended to use cystone, phytolysin or Canephron N. In clinical practice, Canephron N is very convenient for use, which exists in two dosage forms - in the form of drops and dragees, which allows it to be used for the treatment of sporadic dysmetabolic nephropathy even in young children. Canephron N is a medicine containing extracts of centaury, lovage and rosemary. The drug has a complex effect: diuretic, anti-inflammatory, antispasmodic, antimicrobial, thereby increasing the effectiveness of antibiotic therapy, antioxidant and nephroprotective, reduces capillary permeability. The effectiveness and safety of the drug has been proven in a number of foreign and Russian clinical studies. In particular, in a study that included fifty children with dysmetabolic nephropathy, it was found that therapy with Canephron N, compared with treatment with a complex of vitamins (A, E, B6), is more effective and leads in these patients to a more rapid and significant reduction in the frequency of and the severity of hematuria, hyperoxaluria, calciuria and lipiduria [9]. The therapeutic properties of Canephron N are due to its constituent essential oils (lovage, rosemary), phenolcarboxylic acids (rosemary, lovage, centaury), phthalides (lovage), bitters (centaury), ascorbic, pectic, citric and malic acids, and vitamins.

As is known, the main signs of inflammation are associated with the so-called inflammatory mediators (bradykinin, prostaglandins, histamine, serotonin, etc.). The anti-inflammatory properties of Canephron N are mainly due to the antagonism of rosmarinic acid against inflammatory mediators. The mechanism of action is associated with blocking the nonspecific activation of complement, lipoxygenase and cyclooxygenase, followed by inhibition of the synthesis of leukotrienes and prostaglandins. The wide spectrum of antimicrobial action of the drug is due to phenolcarboxylic acids, essential oils, etc. The antimicrobial effect of phenolcarboxylic acids is mediated by the effect on bacterial protein. Lipophilic flavonoids and essential oils are capable of destroying bacterial cell membranes. The diuretic effect of the drug is determined by the combined effect of essential oils and phenolcarboxylic acids. Essential oils dilate the blood vessels of the kidneys, which increases their blood supply. Phenolcarboxylic acids, when released into the lumen of the renal tubules, create high osmotic pressure, which also reduces the reabsorption of water and sodium ions. Thus, an increase in water excretion occurs without disturbing the ion balance (potassium-saving effect).

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