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RISK FACTORS, CLINICAL AND LABORATORY FEATURES AND PREVENTION OF OXALATE NEPHROPATIA IN CHILDREN

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ABSTRACT

In recent years, the frequency of kidney diseases in children, including dysmetabolic nephropathy, has increased, which is associated both with improving the quality of diagnosis and the deterioration of the ecological situation. In this regard, the problem of early diagnosis, the appointment of adequate diet and drug therapy is relevant. The article deals with the problem of etiology, pathogenesis, as well as criteria for the diagnosis of dysmetabolic nephropathy in children. Attention is paid to the clinical manifestations of this pathology and the basic principles of treatment and prevention.

KEYWORDS: *Children, Dysmetabolic Nephropathy, Crystalluria, Oxalaturia.*

INTRODUCTION

Urinary tract diseases are one of the most pressing problems in paediatrics today. Epidemiological studies carried out at the turn of the twentieth to the twenty-first century showed that the incidence of uI diseases varies from 60: 1000 to 187: 1000 children in the child population, depending on the ecological situation in the child's area of residence **[1,7,8].** At the same time in the structure of OMC pathology prevail congenital and hereditary genesis diseases with latent onset and torpid course, among which a large proportion are metabolic, dysmetabolic nephropathies (DN).

Dysmetabolic nephropathies are understood as a large group of nephropathies with different etiology and pathogenesis, but united by the fact that their development is associated with metabolic disorders. Metabolic pathology leads to changes in the functional state of the kidneys or to structural shifts at the level of various elements of the nephron. Dysmetabolic nephropathies in a broad sense are diseases associated with severe disorders of water-salt metabolism, which develop in gastrointestinal diseases with toxic syndrome and haemodynamic disorders. They may include renal damage occurring against a background of impaired phosphorus-calcium metabolism in hyperparathyroidism, hypervitaminosis D and other diseases. The term "dysmetabolic nephropathy", used in a narrow sense, refers to a polygenic inherited (multifactorially evolving) nephropathy that is associated with impaired oxalic acid metabolism and manifests itself in a familial cytomembrane instability.

Healthy children excrete single small salt crystals (most commonly oxalates and tripelphosphates) of 0.03-0.055 μm in the urine, which do not cause renal tissue damage. It is believed that the damaging effect on the urinary system organs is possible in the presence of crystals in the urine sediment more than 10 in the field of view and when their size is more than 12 microns. Three fundamental factors play a role in the process of crystal formation: oversaturation of the tubular fluid beyond its stability limits, reduced activity of oversaturation inhibitors, and the presence of precipitation activators.

Crystalluria is a variant of urinary syndrome in which the laboratory test shows increased salt crystals in the urine. In everyday practice, almost one in three children has this symptom. The proportion of crystalluria in paediatricnephrological pathology exceeds 60% (1). Oxalate and calcium oxalate crystalluria are the most common, accounting for 75.0%-80.0% **[1,2,13].**

For crystal formation, an ionic pair - an anion and a cation (e.g. a calcium ion and an oxalate ion) - must be present. The oversaturation of urine with different kinds of ions eventually leads to their precipitation in the form of crystals and their subsequent growth. The dehydration of the urine plays a major role, which leads to an increase in the concentration of ions in the urine even when they are normally produced. In addition to the degree of saturation, ionic strength, complexing ability, urine flow rate and urine pH influence ion solubility **[14,17].**

The problem of sporadic dysmetabolic nephropathies is highly topical in paediatrics and paediatric nephrology. This is due to the high incidence of the disease in the population and the possibility of its progression up to the development of urolithiasis and/or interstitial nephritis.

Intermittent oxalate-calcium crystalluria in childhood and adolescence has been shown to progress to tubulointerstitial disorders in adults and to increase the incidence of mixed urinary syndrome, characterized by marked proteinuria, haematuria, signs of renal tubular epithelial membranolysis, and functional and structural changes in the kidneys and bladder **[5].**

Among DN associated with disorders of water-salt, carbohydrate, phosphorus-calcium and other types of metabolism, oxalic acid metabolism disorders, the so-called dysmetabolic nephropathies with oxalate-calcium crystalluria (DN with OCC) are the most common, reaching 20% of all OMC pathology, receive special attention **[1,2,5].** Variability in the prevalence of DN with AAC according to different authors is due to differences in the environmental situation in the area where children live and can reach 31.4% in preschool children **[1,3,5].**

Progression of oxalate nephropathy often leads to abacterial interstitial nephritis (IN), and pyelonephritis develops as a result of secondary infection. Maximum dysmetabolic disorders can cause urolithiasis (urolithiasis), even in the early years of life [**3,12,15].**

Currently, the prevalence of crystalluria in children in non-endemic areas is 32%, and in environmentally unfriendly areas it reaches 47%, with oxalate crystalluria accounting for 68-71%, uratecrystalluria for 9-15%, phosphaturia for 9-10% and others ranging from 3 to 5% **[9].**

A clinical and genetic analysis carried out by Ignatova M.S. et al. showed that cases of oxalate nephropathy in an ICD-endemic region can be classified as multifactorial pathology, in which the proportion of hereditary factors is about 60%, environmental - 40% **[10].**

One of the most important scientific and practical areas of social pediatrics and health care organization is the regional approach to the study of children's health. Its formation is influenced

by climatic, geographical, environmental and economic conditions of residence, the degree of population migration, ethnic and socio-cultural characteristics, as well as significant differences in the material and technical base of treatment and preventive care institutions in the regions

According to some experts, dysmetabolic nephropathy with oxalate-calcium crystalluriais considered as a model of eco-dependent disease **[11].**

Pushkareva E. Yu. in studying the clinical and pathogenetic features of the formation and mechanisms of progression of dysmetabolic nephropathies in children depending on age, found that living in areas with high anthropogenic load increases the chance of developing DN with AAC by 2-fold. The author proved that consumption of filtered drinking water can be considered as a preventive measure for the development of oxalate-calcium crypluria in children living in industrial areas **[12].**

The variability in the prevalence of dysmetabolic nephropathy with oxalate-calcium crystalluria according to different authors is due to differences in the environmental conditions in the area where children live and can reach 31.4% **[7,8].** The average prevalence of dysmetabolic nephropathy in Russia is 1.4 in 1,000 children and tends to increase due to the deteriorating ecological environment **[10].**

The most studied factor in the development of dysmetabolic nephropathies in children is the impact of exogenous toxicants: heavy metals, pesticides, components of cement production, which enter the body of children living in environmentally unfriendly regions, as well as in climatically unfavourable seasons of the year during adaptation. Such variants of dysmetabolic nephropathies are called eco-nephropathies **[7].**

There are endogenous and exogenous causes of oxalate dysmetabolic nephropathy in children.Endogenous causes include increased oxalate biosynthesis, hyperuricemia, cystine metabolism disorders, phosphaturia, diabetes mellitus, vitamin metabolism disorders, ischaemic nephropathy, electrolyte disorders, hyperparathyroidism. Exogenous causes include dietary habits, drinking habits, ecopathogens (cadmium, lead, uranium, organic solvents, etc.), medications, climatic features of the region of residence. Persistent crystalluria should be considered a specific sign of impaired calcium metabolism at the cellular level, its presence is usually combined with salt diathesis **[1,2].**

Calcium oxalate crystallisation in the tubulointerstitium, due to its local toxicity and poor solubility, is a trigger mechanism in tubulointerstitial damage **[18].** Damaged cells of the renal epithelium actively bind to the crystals, inducing regeneration and repair processes. Proliferating urothelial cells express "crystal-binding molecules" on their surface, which act as stimulators of crystal adhesion to the surface of epithelial cells **[19,20].**

There are two etiopathogenetic variants of hyperoxaluria - primary and secondary. Primary hyperoxaluria is an inherited disorder involving three rare types of genetically determined disorders of glyoxylic acid metabolism, characterised by increased oxalate excretion, recurrent oxalate-calcium urolithiasis and/or nephrocalcinosis and a progressive decline in glomerular filtration rate with the development of chronic renal failure (2). Oxalate-calcium crystals are deposited in all body tissues, leading to oxalosis at the age of 10-30 years. The disease is inherited by autosomal recessive type, but there are known cases of dominant inheritance. These forms are diagnosed by biochemical methods and their clinical manifestations are identical.

In paediatric practice, the most common is secondary or spontaneous hyperoxaluria, which can be transient (with a monotonous diet, acute respiratory 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].**

Risk factors for secondary hyperoxaluria include a hereditary predisposition, which occurs in 70% of children with hyperoxaluria. This is manifested not only by abnormal oxalate metabolism, but also by but also a predisposition to cytomembrane instability **[13].** 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. Oxalate precursors are formed when acid phospholipids of cell membranes are broken down.

The stages of development of oxalate nephropathy in the progression of renal damage in the age aspect: from oxalate diathesis at an early age to the development of chronic tubulointerstitial nephritis and urolithiasis in adults is shown in the works of M.S. Ignatova et al. (2000, 2006); N.V. Voronina et al. (2000, 2009). In the works of N.V. Voronina it is emphasized that in therapeutic practice this pathology is detected more often in persons of working age, which is latent in childhood and adolescence **[5,6].**

In recent years, the literature has considered oxalate nephropathies as a heterogeneous group of polygenic inherited and multifactorial nephropathies associated with impaired oxalic acid metabolism. The pathology is based on a membranopathological process, usually of a familial nature **[5,6].**

Recently, local oxalate formation in the kidneys has been discussed due to the destruction of cell membrane phospholipids, resulting in oxalate precursors (serine) as well as phosphates, with which calcium forms insoluble salts **[16].**

The first manifestations of hyperoxaluria in children can be as early as the first year of life. Hyperoxaluria is most common during the periods of intensive growth of the child - 7- 8 and 10-14 years of age. In most cases oxalate crystalluria is detected accidentally, sometimes against the background of acute respiratory infections and intercurrent diseases.

Often parents notice that the child has a decrease in urine volume during the day, precipitation of large amounts of salts. When children are interviewed, recurrent abdominal pain is detected. Sometimes genital inflammation develops due to constant irritation of the skin and mucosa, burning sensation or other dysuric disorders may occur during urination. A urinary infection often develops against the background of crystalluria. The urine is visually assessed for saturation, and spontaneous sludge formation may occur. Hyperstenuria (relative urine density above 1030) in the absence of glucosuriashould be suspected of hyperoxaluria. Subsequently, minor microhaematuria and/or proteinuria, abacterialleukocyturia appear against a background of crystalluria, suggesting renal damage and termed "dysmetabolic nephropathy" **[4].**

Biochemical examination of daily urine (salt transport) clarifies the presence of hyperoxaluria and hypercalciuria. Normal levels of oxalate are less than 0.57 mg/kg/day and calcium is less than 4 mg/kg/day. The calcium/creatinine and oxalate/creatinine ratios can also be used to diagnose hyperoxaluria and hypercalciuria **[4].**

In children with hyperoxaluria in nephrological hospitals, urine anti-crystalline calcium oxalate capacity is tested for calcium oxalate, which is reduced. A urine peroxide test assesses the activity of cytomembrane lipid peroxidation processes.

Renal ultrasound reveals echopositive inclusions in the pelvis and calyx in some children.

To prevent DNOCC and calcium nephrolithiasis it is recommended to monitor children from families with hereditary predisposition to urolithiasis, with regular preventive treatment including diet therapy, drinking regime, vitamin therapy (A, E, B6) and other treatments, especially phytotherapy.

The authors Dlin V.V., Ignatova M.S., Osmanov I.M., Yurieva E.A., Morozov S.L. (2015) prove that 5-year follow-up of 130 children showed the effectiveness of this rehabilitation scheme both in the treatment and prevention of relapses of pyelonephritis and in reducing the severity of metabolic disorders in children.

Despite recent advances in the treatment of dysmetabolic nephropathies, the problem of improving treatment methods, preventing the most severe outcomes of the disease, the introduction of effective preventive measures is still one of the most important in modern paediatric nephrology.

The versatility of pathogenetic mechanisms of damage to the urinary system, the severity of consequences caused by metabolic disorders, such as urolithiasis, pyelonephritis, etc., focus scientists to search for new modern technologies of treatment and prevention of these diseases.

Thus, study of risk factors and basic etiopathogenetic mechanisms of dysmetabolic nephropathy formation in children is of particular importance because of their high prevalence and severe prognosis.

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