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THE INFLUENCE OF GENETIC FACTORS ON THE DEVELOPMENT OF UROLITHIASIS IN CHILDHOOD

Abstract: *Urolithiasis is a widespread disease among both adults and children. Children make up 2-5%. Countries such as India, Turkey, Pakistan, Iran, some countries of South Asia, Africa and the northern states of the USA are endemic.*

The incidence of urolithiasis among the children's population of Uzbekistan tends to increase. Thus, according to statistics, over a thousand new cases have been detected annually in the last 5 years. The prevalence of urolithiasis among children is 2-5%. Among boys, the disease is more common - 1:2-1:4 than among girls. This article presents the features of the influence of the genetic factor on the development of urolithiasis

Key words: *urolithiasis, metaphylaxis, genetics, vitamin D, children.*

Language: *Russian English*

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Introduction

Purpose of the article: to study the features of the influence of genetic factors on the development of urolithiasis in childhood

Urolithiasis in children is a serious disease that requires surgical treatment in most cases. Stone formation encourages doctors to resort to surgical, in some cases repeated intervention, which is accompanied by a high level of complications and recurrence and leads to a rapid decrease in kidney function, disability of children. The problem of child disability remains extremely relevant for all civilized countries of the world and is an indicator of the health status of the child population. The search and finding of the causes of stone formation, sparing methods of removing concretions and adequate metaphylaxis are the main directions of modern study of urolithiasis worldwide (5, 8, 11, 18, 32, 42).

The cause of urolithiasis can be detected in 67-92.6% of cases. Currently, there are two groups of factors for the development of urolithiasis: exogenous and endogenous (29, 32, 38, 42, 45).

Exogenous factors include ecology, lifestyle of parents, burdened gynecological history, living in a

hot climate, race, gender and age of the child, eating food rich in animal protein, high-calorie diet, taking medications. Endogenous factors include abnormalities of the structure of the organs of the urinary system, urinary infection, metabolic disorders, heredity and genetic predisposition.

These are factors that have been well studied and are beyond doubt. However, it is important to note that many researchers in recent years have come to the conclusion that genetic predisposition to metabolic disorders associated with the metabolism of stone-forming substances is the main determinant of the development of urolithiasis, while environmental and dietary factors that play an important role in the development of urolithiasis in adults remain insignificant in children.

The hereditary factor of the development of urolithiasis is increasingly widely discussed in modern literature. The family history of the disease can be traced in 46-83% of cases and is least pronounced in European countries (12-33% of cases); in North American children, this indicator 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 metabolic disorders of lithogenic substances has been proved (4, 5, 9, 27, 34, 35, 38, 50, 51).

Modern urology has a significant arsenal of methods for ridding most patients of kidney stones and urinary tract. However, removing a stone does not mean getting rid of urolithiasis. That is why the problems of metaphylaxis (prevention of relapse) of urolithiasis are extremely relevant. The treatment of most conditions in which stones form in the urinary organs is currently based primarily on symptoms, not on causes. In this regard, it is relevant to study the distribution of genotypes of polymorphic markers of vitamin D receptor (VDR) genes in children with and without urolithiasis.

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. Of great importance in the diagnosis of urolithiasis is the identification of the degree of involvement of genetic factors. The results of the study and the literature data showed that the occurrence of metabolic disorders characteristic of urolithiasis is significantly influenced by hereditary predisposition in combination with environmental factors.

The realization 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 ICD is the vitamin D receptor gene.

The vitamin D receptor is encoded by the VDR gene, which is characterized by genetic polymorphism, that is, the existence of various allelic variants of this gene in the population. The most significant polymorphisms of the VDR gene involved in the development of diseases were: Bsm I, For I, Tag I. Several studies have established the association of polymorphism of the VDR gene with urolithiasis. Published data demonstrating the significance of the presence of the ApalAA genotype, which determines sensitivity to vitamin D, in the development of calcium stones in the urinary organs. It is also reported that the incidence of HLA B13, B22 and B35 genes in patients with urolithiasis is higher than in healthy individuals.

Studies conducted by a number of foreign scientists have shown that metabolic disorders of phosphorus metabolism lead to hypophosphatemia and often associated hypercalciuria and urolithiasis. This disorder was found to be associated with two different heterozygous mutations in the renal protein transporting sodium phosphate encoded as the NPT2*a* gene. Each of the destroyed genes has been identified. Such disorders were found in patients with recurrent urolithiasis and decreased renal phosphate reabsorption. Interestingly, other genetic forms of urolithiasis associated with hypophosphatemia were established without the presence of mutations in the NPT2*a* gene of the same name. All these disorders have a very high level of the active vitamin D product of the endocrine system, 1,25-dihydroxyvitamin D. Such high levels of 1,25-dihydroxyvitamin D may contribute to a higher than usual efficiency of calcium absorption through the gastrointestinal tract and a decrease in the synthesis and secretion of parathyroid hormone. Such physiological changes in calcium homeostasis speak in favor of hypercalciuria and thus may contribute to the formation of kidney stones.

Despite many population-based molecular genetic studies, the molecular genetic markers of urolithiasis in children are still insufficiently studied. Also, the issues of the choice of diet therapy, as well as the effectiveness of diet therapy, depending on the genetic status of the patient, have not been sufficiently studied. The pharmacogenetic aspects of urolithiasis, such as the choice of pharmacological drugs for conservative treatment and metaphylaxis of urolithiasis, depending on the genetically determined functional features of metabolism, are also insufficiently studied.

The method of predicting the occurrence of urolithiasis, based on the identification of molecular genetic markers based on DNA analysis, has certain and significant advantages. The biochemical method used for these purposes to determine the violation of

mineral metabolism allows, first of all, to diagnose an existing disease, that is, it is effective for a sufficiently long pathological process. Meanwhile, it was found that even in the presence of an obvious disease, biochemical changes are detected only in half — two thirds of the subjects.

The molecular genetic method of predicting the occurrence of urolithiasis makes it possible to identify a predisposition to the disease at any age, almost from the birth of a person, since the genotype of a particular individual does not change during life. In addition, a predisposition to the disease can be established using this method in the absence of any clinical or biochemical manifestations, that is, at the earliest preclinical stage of pathology development. This means that the earlier the presence of a genetic marker is detected, the more reliable and timely measures to prevent the disease will be.

Thus, such seemingly unimportant risk factors as: the environmental situation in the place of direct residence of patients' families, the lifestyle of parents, the burden of the gynecological history of the expectant mother and the nature of intercurrent diseases of the child itself can lead in some cases to the formation of various kinds of abnormalities of the urinary system in children, impaired metabolism of stone-forming substances and the development of a serious disease - urolithiasis.

Children with a family history of urolithiasis, whose mothers during pregnancy and lactation had risk factors for the development of urolithiasis, suffering from urological diseases or diseases accompanied by metabolic disorders of stone-forming substances, from birth need the close attention of specialists to the state of their urinary system. When detecting abnormalities of the urinary system (ureteral stricture, vesicoureteral reflux, ureterocele, etc.) and metabolic disorders of stone-forming substances, a comprehensive approach to treatment is necessary in each case, which requires the interaction of specialists of different profiles (urologists, endocrinologists, gastroenterologists, nutritionists, geneticists, surgeons) (5, 32, 35, 50).

The complexity of studying urolithiasis is a consequence of the diversity of pathophysiological processes. Although the chemical nature of stones has been known for centuries, and it is known that stones are usually well formed, have a crystalline structure, until recently, it is less known why they are formed and how this process occurs.

It is important to note that many researchers in recent years have come to the conclusion that genetic predisposition to metabolic disorders associated with the metabolism of stone-forming substances is the main determinant of the development of urolithiasis, while environmental and dietary factors that play an important role in the development of urolithiasis in adults remain insignificant in children (27, 32, 48).

The study of the role of genetic factors and the deepening of knowledge in the field of molecular mechanisms underlying the formation of urine components, 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.

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

Conclusion.

Thus, the main directions of studying urolithiasis all over the world are the search and finding of the causes of stone formation, sparing methods of removing concretions and adequate metaphylaxis. In recent years, the accumulation of knowledge in the field of molecular genetics has made it possible to explain the mechanisms of the development 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 a predisposition to the disease at the preclinical stage at any age, practically from the birth of a person, since the genotype of a particular individual does not change during life. The earlier the presence of a genetic marker is detected, the more reliable and timely measures to prevent the disease will be.

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