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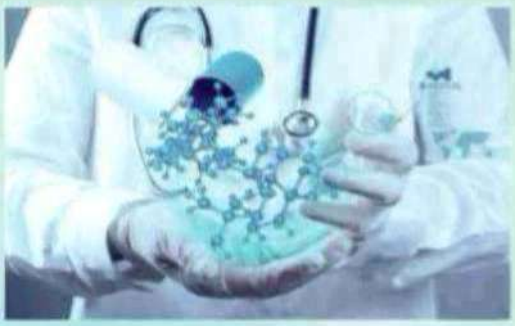

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IMPROVING THE DIAGNOSIS OF UROLITHIASIS IN CHILDREN IN PRIMARY HEALTH CARE

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✓ ***Resume***

Urolithiasis is a very common disease in both adult and paediatric populations and represents not only a social and demographic but also an economic problem.

Aim. To identify polymorphisms of genes associated with the development of urolithiasis in children of the Uzbek population.

Material and methods. The study was conducted in the Specialised Children's Surgical Clinic of Samarkand State Medical University in two stages, in the period from 2012-2019. At the first stage, a retrospective analysis of the case histories of 652 admissions was carried out. At the second stage, a prospective study of 200 children aged from 1 to 17 years, of whom 100 children were diagnosed with urolithiasis (main group), and 100 children in the control group, who did not have urolithiasis, was conducted. Immunogenetic studies of vitamin D receptor (VDR), IL-1β, urokinase genes were performed.

Results: the obtained results suggest that variants of vitamin D receptor (VDR), IL-1β and urokinase genes play an important role in the development of urolithiasis. A statistically significant association of F/f+f/f genotypes of the VDR gene (Fok-1) with urolithiasis was found in the studied groups, which was 1.3 times more frequent in the main group than in the control group. A statistically significant C/C allele of the IL-1β gene and urokinase 3'-UTR T/C was also detected in the main group.

Conclusion: the role of immunogenetic method of urolithiasis prognosis in the detection of predisposition to the disease with the study of the distribution of genotypes of polymorphic markers of genes of vitamin D receptor (VDR), interleukin-1β and urokinase, which proves the importance of immunogenetic factors in the pathogenesis of urolithiasis development in children of Uzbek population, which are predictors of its development at the preclinical stage of the disease.

Key words: urolithiasis in children, early diagnosis, prognosis, risk factors, genetic factors, prelithiasis, primary health care.

СОВЕРШЕНСТВОВАНИЕ ДИАГНОСТИКИ УРОЛИТИАЗА У ДЕТЕЙ В УЧРЕЖДЕНИЯХ ПЕРВИЧНОЙ МЕДИКО-САНИТАРНОЙ ПОМОЩИ

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✓ ***Резюме***

Мочекаменная болезнь является очень распространенным заболеванием, как среди взрослого, так и среди детского населения, представляя собой не только социально-демографическую, но и экономическую проблему.

Цель. Выявить полиморфизмы генов, ассоциированные с развитием мочекаменной болезни у детей узбекской популяции.

Материал и методы. Исследование проводилось в специализированной детской хирургической клинике Самаркандского государственного медицинского университета в два этапа, в период с 2012-2019 гг. На первом этапе был проведен ретроспективный анализ историй болезни 652 поступивших пациентов. На втором этапе проведено проспективное исследование 200 детей в возрасте от 1 года до 17 лет, из них 100 детей с диагнозом мочекаменная болезнь (основная группа) и 100 детей контрольной группы, у которых мочекаменная болезнь не выявлена. Проведены иммуногенетические исследования генов рецептора витамина D (VDR), IL-1β и урокиназы.

Результаты исследования свидетельствуют о том, что варианты генов рецептора витамина D (VDR), IL-1β и урокиназы играют важную роль в развитии мочекаменной болезни. В исследуемых группах выявлена статистически значимая ассоциация F/f+f/f генотипов гена VDR (Fok-1) с мочекаменной болезнью, которая в основной группе встречалась в 1,3 раза чаще, чем в контрольной. В основной группе также выявлен статистически значимый аллель C/C гена IL-1β и T/C урокиназы 3'-UTR.

Заключение: показана роль иммуногенетического метода прогнозирования мочекаменной болезни в выявлении предрасположенности к заболеванию с изучением распределения генотипов полиморфных маркеров генов рецептора витамина D (VDR), интерлейкина-1β и урокиназы, что доказывает значение иммуногенетических факторов в патогенезе развития мочекаменной болезни у детей узбекской популяции, которые являются предикторами ее развития на доклинической стадии заболевания.

Ключевые слова: мочекаменная болезнь у детей, ранняя диагностика, прогноз, факторы риска, генетические факторы, прелитиаз, первичная медико-санитарная помощь.

BIRLAMCHI TIBBIY-SANITARIYA MUASSASALARIDABOLALARDAGI UROLITHIAZNING DIAGNOSTIKASINI TAKOMILLASHTIRISH

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✓ ***Rezyume***

Urolitiaz kattalar va bolalar orasida juda keng tarqalgan kasallik bo'lib, nafaqat ijtimoiy-demografik, balki iqtisodiy muammoni ham ifodalaydi.

Maqsad. O'zbek populyatsiyasi bolalarida urolitiyoz rivojlanishi bilan bog'liq gen polimorfizmlarini aniqlash.

Materiallar va usullar. Tadqiqot Samarqand davlat tibbiyot universitetining ixtisoslashtirilgan bolalar jarrohlik klinikasida 2012-2019 yillar davomida ikki bosqichda o‘tkazildi. Birinchi bosqichda qabul qilingan 652 nafar bemorning tibbiy hujjatlari retrospektiv tahlil qilindi. Ikkinchi bosqichda 1 yoshdan 17 yoshgacha bo'lgan 200 nafar bolada istiqbolli tadqiqot o'tkazildi, ulardan 100 nafar bolaga urolitiyoz (asosiy guruh) tashxisi qo'yilgan va nazorat guruhidagi 100 nafar

bolada urolitiaz aniqlanmagan. D vitamini retseptorlari (VDR), IL-1β va urokinaz genlarining immunogenetik tadqiqotlari o'tkazildi.

Tadqiqot natijalari shuni ko'rsatadiki, D vitamini retseptorlari (VDR), IL-1β va urokinaza genlaridagi variantlar urolitiazning rivojlanishida muhim rol o'ynaydi. Tadqiqot guruhlarida VDR genining (Fok-1) F/f+f/f genotiplarining urolitiaz bilan statistik jihatdan ahamiyatli assotsiatsiyasi aniqlandi, bu tadqiqot guruhida nazorat guruhiga qaraganda 1,3 marta tez-tez uchraydi. Asosiy guruhda IL-1β geni va T / C urokinaza 3'-UTR ning statistik ahamiyatga ega C / C alleli ham aniqlandi.

Xulosa: kasallikka moyillikni aniqlashda urolitiazni bashorat qilishning immunogenetik usulining roli D vitamini retseptorlari (VDR), interleykin-1β va urokinaza genlarining polimorf markerlari genotiplarining tarqalishini o'rganish orqali ko'rsatilgan. Bu o‘zbek populyatsiyasi bolalarida urolitiyoz rivojlanishining patogenezida immunogenetik omillarning ahamiyatini isbotlaydi va kasallikning klinikgacha bo‘lgan bosqichida rivojlanishini bashorat qiluvchi omillardir.

Kalit so'zlar: bolalarda urolitiyoz, erta tashxis, prognoz, xavf omillari, irsiy omillar, prelitiyoz, birlamchi tibbiy yordam.

Introduction

Urolithiasis is not only a medical problem, but also a serious socio - economic and demographic problem. The incidence of urolithiasis is increasing worldwide. The disease, which used to be first detected in adults, is now found in children of all ages. According to the World Health Organisation (WHO) '...urinary tract diseases are the second most frequent pathology of childhood. Over the last decade, the incidence of urinary tract diseases in children has increased 2.5-3 times and ranges from 20.6 to 106.0 per 1000 child population, depending on the region. Changes in the nature of nutrition and physical activity of children lead to changes in the metabolic status of the organism, and predisposition factors to urolithiasis are realised already in childhood'.

The available epidemiological data on the prevalence of urolithiasis indicate that this pathology occurs on all continents, with different levels of incidence. Exogenous risk factors for the development of urolithiasis are hot and dry climate, certain chemical composition of soil and plants, the degree of saturation of water with mineral salts, climatic conditions, gender and age peculiarities, industrial and social conditions; and endogenous - congenital and acquired kidney anomalies, urinary tract infections, gastrointestinal diseases, bone trauma with prolonged immobilisation, parathyroid gland hyperfunction, genetic predisposition [1, 2]. Despite the fact that all over the world special attention is paid to scientific research devoted to the study of etiology, risk factors, mechanisms of development, diagnosis and differential diagnosis, as well as effective methods of treatment and prevention, unfortunately, to date there are not enough works devoted to early diagnosis of urolithiasis, especially in children, taking into account the identification of risk factors in outpatient and polyclinic conditions.

Traditionally, urolithiasis was considered a disease of adults. However, nowadays there is more and more data on the significant growth of this pathology in children. It should also be noted that this pathology in children differs from that in adults. This causes a special interest to this problem and the need to study epidemiological processes by sex and age categories, as well as in the regional context with the definition of etiological risk factors of urolithiasis. Later, this will make it possible to develop therapeutic and preventive, diagnostic measures, the main goal of which is timely treatment and reduction of morbidity [3, 4].

A characteristic feature of urinary stone disease is its asymptomatic course, so for a long time the patient does not seek medical help, despite the possibility of early diagnosis of the disease [5]. Most researchers have noted the presence of stone formation detected at autopsy, which also indicates the fact of asymptomatic course of the disease in a significant number of patients [6, 7].

According to some studies, due to the development of renal colic, about one third of patients with urolithiasis require emergency surgical interventions, but stones may be absent on examination, although their exit has not been noted by patients [8, 9].

There are many different methods of kidney and urinary tract stone removal in the arsenal of modern urology. But, unfortunately, removal of a stone does not mean getting rid of urolithiasis, as one of the characteristic features of the disease is the occurrence of recurrence. That is why one of the urgent problems today is the early diagnosis of this pathology [10, 11].

Statistical reports of most countries provide data on the financial burden of urolithiasis, which tends to increase. As the authors show, in economically developed countries, the average cost of care for patients with urinary stone disease among adults is more than 10 billion dollars per year [12]. The costs associated with hospitalisation with urolithiasis in children also tend to increase annually, with an average of more than $18,000,000 spent on inpatient care [13].

If we consider the causative factors and mechanisms that determine the risk of developing urolithiasis in the pediatric population, we can say that they remain unexplored, although there are many hypotheses and theories (about 200) of urinary stone formation [14].

Over the last twenty years, in their epidemiological and clinical studies, scientists increasingly point to the involvement of genetic factors in the occurrence of urolithiasis, which indicates the existence of certain genes responsible for the development of this pathology [15].

To predict the occurrence of urinary stone disease and to develop ways of its prevention in children, it is necessary to study immunogenetic aspects of the disease and search for markers of predisposition to urolithiasis. This will increase the effectiveness of therapeutic and preventive measures, reduce the number of complications and improve the quality of life of patients [16].

Genetic research methods help not only in the processes of diagnosis and treatment, but also increase the possibility of predicting diseases that may develop in a person during life. Thus, genes whose polymorphisms can lead to diseases such as breast and ovarian cancer, arterial hypertension, diabetes mellitus, etc., are now well studied.

Summarising the available data, we can conclude that the main directions of urolithiasis research all over the world are the search and finding the causes of stone formation, gentle methods of concrement removal and adequate metaphylaxis. In recent years, the accumulation of knowledge in the region of molecular genetics has allowed to explain the mechanisms of urolithiasis development, which has led to a new era of diagnostics and treatment of this pathology.

The peculiarity of the genetic method of diagnostics of the disease, unlike traditional studies, is the possibility of predicting the occurrence of urolithiasis at the preclinical stage at any age. This is due to the fact that the human genotype does not change during life. In this regard, in order to achieve our goals, it is relevant to study the distribution of genotypes of polymorphic markers of genes-predictors of urolithiasis development in children of the Uzbek population.

Purpose of the study: To identify polymorphism of genes associated with the development of urolithiasis in children of Uzbek population.

Material and methods

The study of urolithiasis prevalence was carried out according to the data of referral to the Specialised Children's Surgical Clinic of Samarkand State Medical University in the period from 2012 to 2019. The work was carried out in two stages.

At the first stage, to study the prevalence of urolithiasis and to determine the risk factors, we analysed the medical records of 652 patients aged 1 to 17 years who came to the hospital with the diagnosis of urinary stone disease. At the second stage of the study, in order to fulfill the set tasks of studying immunogenetic predisposition to urolithiasis development in children, a clinical examination of 200 children who were divided into two groups was carried out.

The first (main) group consisted of 100 patients with urolithiasis who underwent a comprehensive examination (clinical, haematological, biochemical, ultrasound, radiological, immunogenetic) and treatment. The second (control) group consisted of 100 children without urolithiasis and hospitalised for minor planned surgical interventions (circumcision, herniotomy) at the Specialised Children's Surgical Clinic of Samarkand State Medical University. Among the patients, the majority of patients with urolithiasis are children over 5 years of age, more often aged 5-9 years - 63 (63%). By sex distribution in the main group, urolithiasis is more common among boys - 68 (68%) children than among girls - 32 (32%).

The immunogenetic study was conducted in the laboratory of genomics of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan. Blood samples were collected from all 200 patients of both groups. The material for DNA extraction was venous blood from the cubital vein in the volume of 1 ml. Disposable plastic tubes with 0.5 ml preservative were used for collection, storage and transport of blood. Blood was stored at +4°C for further processing.

DNA extraction from whole blood was performed according to the standard protocol using Diatom™ DNA Prep 200 reagent kit (IsoGen Laboratory LLC, Moscow, Russia).

The Ethics Commission of Samarkand State Medical University approved this study (IRB protocol № 2023-0001 dated 12 August 2023).

Statistical analysis of the obtained data was carried out with the help of statistical on-line calculators (https://medstatistic.ru/calculators). The data are presented in the form of fractions. Comparison of the main and control groups was performed by the χ^2 criterion for a 4-field table at df=1 and by the χ^2 criterion for arbitrary tables at df >1. Differences were considered statistically significant at $p<0.05$.

Result and discussions

Results of VDR gene polymorphism study. Table 1 shows the genotype distribution of the VDR FokI polymorphism in children with urolithiasis (main group) and in the control group.

Table 1

Results of the distribution of the association of the VDR gene with urolithiasis in children of the main and control groups according to the dominant model of inheritance.

Genotypes/ alleles	Main group, n=100	Control group, n=100	χ^2	p
Genotype F/F	37	52	=4,56	=0,033
Genotype F/f+f/f	63	48		
F- allele	65	73		
f- allele	35	27		

Note: p - statistical significance of differences between the main and control groups (according to the χ^2 criterion)

As can be seen from Table 1, a statistically significant association of F/f+f/f VDR (FokI) genotype was found in the studied groups, which was 1.3 times more frequent in the main group than in the control group. However, in the control group the frequency of occurrence of the F/f+f/f genotype was 48%, which indicates the frequency of occurrence of the studied allelic variants also in children without urolithiasis, thus influencing the formation of predisposition to the disease in this group.

Thus, a comparative analysis of the frequency distribution of FokI genotypes of the VDR gene polymorphism revealed a statistically significant association of the f allele with urolithiasis. This fact suggests that the presence of Ff+ff genotypes may indicate a significantly high risk of urolithiasis development in children and may serve as a criterion for predicting the development of urolithiasis in children.

Results of the IL-1β gene polymorphism study. Further, genotyping of IL-1β gene was performed in the main (children with urolithiasis, n=100) and control (children without urolithiasis, n=97) groups, and comparative analysis of the obtained results was performed. It should be noted that in the study of this gene the number of children in the control group was 97 instead of 100, which was due to technical moments of immunogenetic analysis.

Table 2 presents the data on the distribution of IL-1β gene polymorphism genotypes in children with urolithiasis and in the control group.

Table 2

Results of the distribution of the association of the IL-1β gene association with urolithiasis in children of the main and control groups according to the common inheritance model

Genotypes/ alleles	Main group, n=100	Control group, (n=97)	χ^2 (df=2)	p
Genotype T/T	29	23	=7,23	=0,027
Genotype T/C	44	60		
Genotype C/C	27	14		
T- allele	51	53		
C- allele	49	44		

Note: p - statistical significance of differences between the main and control groups (according to the χ^2 criterion for arbitrary tables).

Thus, when determining the IL-1β gene polymorphism in the control group, the T/C genotype was the most frequent - 61.9%. Whereas the detection rate of T/T genotypes was higher in the main group compared to the control group, being 29.0% versus 23.7%. The most significant marker of stone formation in children was the C/C genotype, which was 1.9 times more frequent than in children of the control group.

The results of statistical analysis of the distribution of genetic association of IL-1β gene genotypes with urolithiasis when comparing the main group with the control group showed a difference only for the C/C genotype ($p<0.05$).

Table 3 shows the data on the distribution of IL-1β gene polymorphism genotypes in the main and control groups under recessive inheritance model.

Table 3

Results of the distribution of the association of IL-1β gene with urolithiasis in children of the main and control groups according to the recessive inheritance model

Genotypes	Main group, (n=100)	Control group, (n=97)	χ^2	p
Genotype T/T+T/C	73	83	=4,72	=0,030
Genotype C/C	27	14		

Note: p - statistical significance of differences between the main and control groups (according to the χ^2 criterion for arbitrary tables).

As follows from the table 3, the recessive model of inheritance showed the same pattern as the dominant model ($p<0.05$).

Thus, the comparative analysis of the frequency distribution of IL-1β gene genotypes in the main group showed a statistically significant association of C/C genotype with urolithiasis. This indicates that the C/C-genotype of IL-1β influences the formation of predisposition to stone formation in children in any inheritance model.

Molecular genetic study of the 3'-UTR T/C polymorphism of the urokinase gene. The urokinase gene encodes urokinase plasminogen activator, which is a serine proteinase. This gene is synthesised mostly in kidney cells. Urokinase promotes the cleavage of plasminogen into plasmin, which in turn stimulates the production of fibrinolysis. According to some authors, urokinase plays a major role in the formation of urinary stones.

When analysing the distribution of variant genotypes of the 3'-UTR T/C polymorphism of the urokinase gene, a statistically significant p=0.03 for the common model of inheritance and p=0.01 for the dominant model of inheritance, an increase in the frequency of monozygotes T/T and heterozygotes C/T in patients compared with the corresponding indicators in the control group was found.

Table 4

Results of statistical analysis of genetic association of urokinase gene genotypes in groups of examined children

Genotypes	Main group, n=100	Control group, n=94	χ^2	p
General inheritance model (χ^2 test, df = 2)				
C/C	41	56	6,77	0,03
C/T	49	34		
T/T	10	4		
Dominant inheritance model (χ^2 test, df = 1)				
C/C	41	56	5,94	0,01
C/T+T/T	59	38		

In determining the influence of the dominant genotype of the 3'-UTR T/C polymorphism of the urokinase gene in relation to dysmetabolic disorders, we found that carriers of the T allele had the highest incidence of uraturia (χ^2=6.8; P=0.01; OR=1.8; 95% CI 1.14-2.7) have a high incidence of uraturia, as well as in carriers of heterozygous C/T genotype and homozygous T/T genotype of the studied urokinase gene polymorphism.

Thus, the results obtained in this study indicate that genetic variants of the urokinase gene polymorphism labelled as 3'-UTR T/C contribute to the determination of disorders contributing to the development of urolithiasis in children.

Observation

Urolithiasis is a multifactorial disease, in the development of which not only environmental factors but also hereditary predisposition play an important role. In addition, it is a widespread disease, the number of cases of which continues to steadily increase in both adult and paediatric populations. More and more often there are data on the incidence of urolithiasis among young children and even newborns. It is believed that the main causative factors for the development of the disease are hot climate, high level of blood marriages, as well as genetic and racial features. The lack of complete epidemiological information occurs in almost every country, and therefore, these data have significant differences, which may be due to imperfect methodological approaches and information collection [17].

Most scientists believe that, first of all, it is related to changes in the nature of nutrition, the ecological situation in the world, the quality of consumed liquids and food [18, 19]. Some authors argue that lifestyle changes affect the increase in the incidence of urinary stone disease [20-22]. Other researchers in their conclusions insist that the reason for the sharp increase in the incidence of urolithiasis in different populations is the increased incidence of mutations and polymorphisms of certain genes [23].

In the last decade, scientists have increasingly investigated the relationship between various genes and urolithiasis. Despite many population-based immunogenetic studies, the markers that play a major role in the development of urolithiasis in children are still poorly understood. The possibility of predicting the occurrence of urinary stone disease based on the detection of immunogenetic markers has definite promise. Knowledge of possible predisposition to urolithiasis development, which can be determined using immunogenetic markers at an early preclinical stage, will allow timely prevention of the disease and initiation of adequate treatment [24].

Our study of VDR, interleukin-1β and urokinase 3'-UTR T/C gene polymorphisms indicates a high risk of stone formation in children. At the same time, the analysis of the association of IL-18 +105A/C gene polymorphism with predisposition to urolithiasis development in children under different inheritance models, in particular, dominant and recessive, showed the absence of statistical significance. So, genetic markers of predisposition to urinary stone disease development in children are genotypes Ff+ff of VDR gene, genotype C/C of interleukin-1β gene and polymorphism of urokinase gene labelled as 3'-UTR T/C. These indicators can serve as a criterion for predicting the development of urolithiasis in children at the preclinical stage of the disease.

Conclusion

Thus, polymorphism of VDR and interleukin-1β genes indicates a high risk of stone formation in children. In particular, genotypes Ff+ff of the VDR gene, C/C of the interleukin-1β gene and urokinase 3'-UTR T/C are genetic markers of predisposition to ICH development in children. These parameters can serve as criteria for predicting the development of urolithiasis in children at the preclinical stage of the disease. Consequently, it is reasonable to include testing to detect the presence of these genotypes in children at high risk of urinary stone disease development living in Uzbekistan in the programme of early diagnosis of urolithiasis in primary health care.

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