



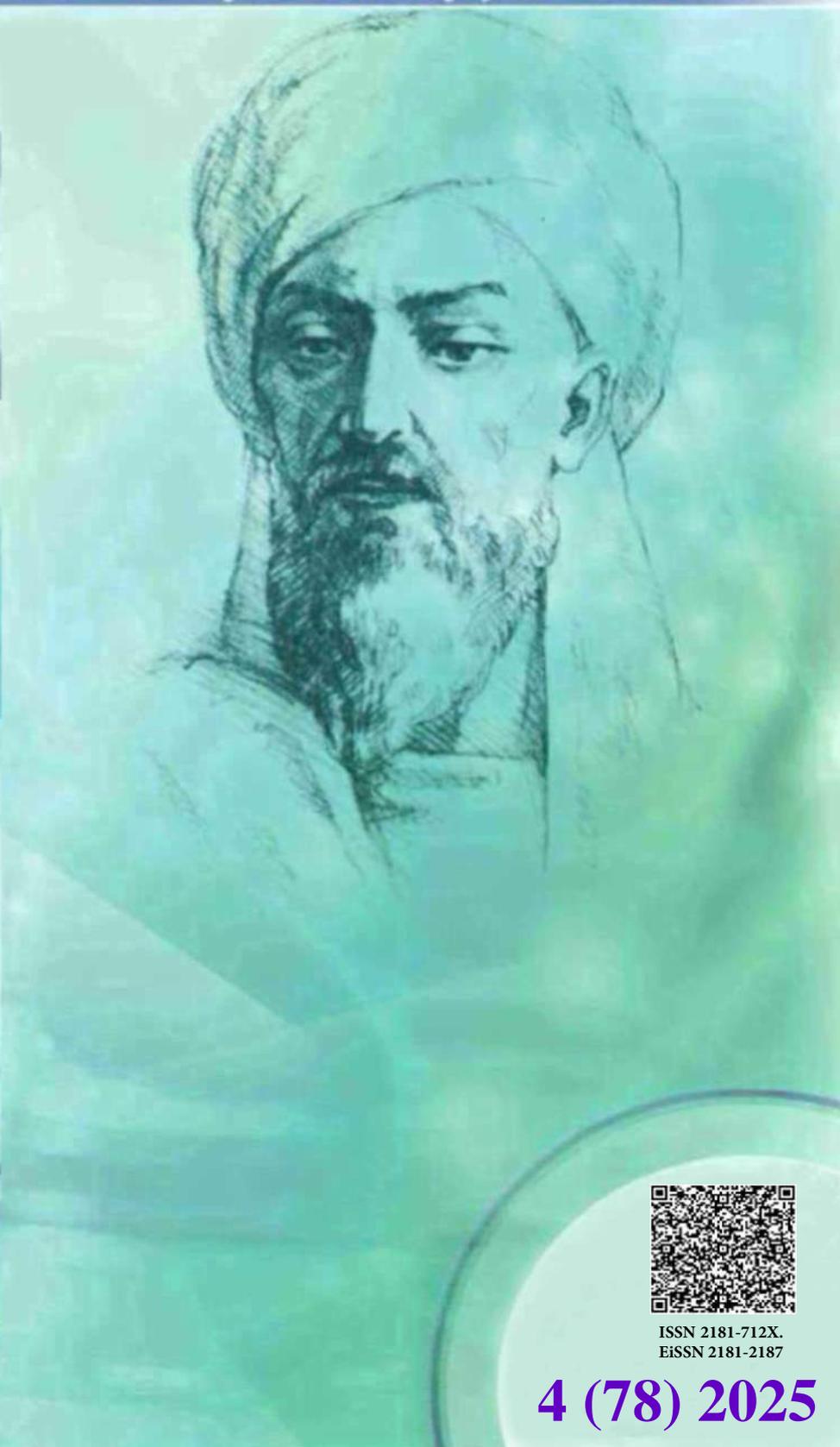
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**ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE**

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A PERSONALISED APPROACH TO THE MANAGEMENT OF CHILDREN WITH UROLITHIASIS IN A PRIMARY HEALTH CARE

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Today urolithiasis is not only a medical problem, but also a serious socio-economic and demographic problem. Therefore, it is very important to timely identify risk factors for the spread of urolithiasis in the population and implement measures aimed at preventing complications, as well as the subsequent increase in the range of medical and social care, reducing disability and improving the quality of life.

Objective. To develop a scientifically based algorithm for prediction and early diagnosis of urolithiasis in children in primary health care.

Material and methods. The study included children (n=100) with urolithiasis - the main group, relatively healthy children (n=100) - the control group; and their parents. Using the developed questionnaire, an in-depth analysis was carried out to assess the life history of children and their parents, taking into account the course of pregnancy in the mother, the presence of chronic diseases of the parents, as well as the status of stone-forming substances, that is biochemical studies of blood and urine.

Results. The developed algorithm for early diagnosis and prognosis of urolithiasis in children in a polyclinic will allow to identify the risk group with the construction of a personalised approach to patient routing at the stages of observation. Children scoring from 4 to 6 points and included in the average risk group also require clinical, laboratory and instrumental investigations. Patients found to have clinical and/or laboratory and instrumental changes in urolithiasis should be referred to a paediatric urologist in a specialised clinic for further comprehensive examination and treatment. If the results of clinical, laboratory and instrumental methods of investigation do not reveal signs of urolithiasis, immunogenetic analysis is recommended. The analysis of the conducted studies has shown that patients with high risk of urolithiasis development (from 7 to 10 points), require special attention. If clinical signs of the disease are detected in children, they are referred to a paediatric urologist of a specialised clinic. In the absence of clinical signs of urolithiasis, laboratory and instrumental investigations should be performed. Children with relevant changes in laboratory tests and ultrasonography of the urinary tract should be referred to a paediatric urologist in a specialised clinic. In the absence of changes in laboratory tests and ultrasound data, immunogenetic testing is performed. Children with a high risk of developing urolithiasis and in the presence of gene polymorphism there is a need for a set of measures to prevent the development of urinary stone disease. In cases where changes at the gene level are not detected, children should be under the supervision of a doctor in an outpatient clinic.

Conclusion. The developed algorithm of early diagnosis and prediction of urolithiasis development in children in the conditions of primary care will allow to identify the risk group with the construction of a personalised approach to the patient's routing at the stages of observation.

Key words: urolithiasis in children, prediction, early diagnosis, genetic factor, prelithiasis, diagnostic algorithm.

ПЕРСОНИФИЦИРОВАННЫЙ ПОДХОД ВЕДЕНИЯ ДЕТЕЙ С УРОЛИТИАЗОМ В УСЛОВИЯХ ПОЛИКЛИНИКИ

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✓ Резюме

На сегодняшний день мочекаменная болезнь (МКБ) представляет собой не только медицинскую, но также серьёзную социально-экономическую и демографическую проблему. Поэтому очень важно своевременно выявлять факторы риска распространения уролитиаза среди населения и осуществлять мероприятия, направленные на предупреждение осложнений, а также последующее повышение спектра медико-социальной помощи, снижение инвалидности и улучшение качества жизни.

Цель. Разработать научно-обоснованный алгоритм прогнозирования и ранней диагностики мочекаменной болезни у детей в условиях поликлиники.

Материал и методы. В исследование включены дети (n=100) с МКБ – основная группа, относительно здоровые дети (n=100) – контрольная группа; и их родители. С помощью разработанного анкетного-опросника проведен углубленный анализ по оценке анамнеза жизни детей и их родителей с учетом течения беременности у матери, наличия хронических заболеваний родителей, а также статуса камнеобразующих веществ, т.е. проведение биохимических исследований крови и мочи.

Результаты. Основываясь на результатах исследовательской работы был разработан алгоритм ранней диагностики и прогнозирования развития уролитиаза у детей на доклинической стадии заболевания в условиях поликлиники с учётом факторов риска и иммуногенетической предрасположенности. Согласно алгоритму, оценка степени риска развития уролитиаза при проведении первого действия основывается на анамнестических данных и анализе факторов риска. Для этого разработано 10 основных вопросов, на основании которых индивидуально для каждого ребёнка можно выявить степень риска по 10-и балльной шкале. Суммируя полученные результаты, прогнозируется степень риска развития уролитиаза. При выполнении второго действия разработанного алгоритма проводится маршрутизация пациентов в зависимости от соотношения их к той или иной степени риска развития МКБ. Так, дети, набравшие согласно 10-ти балльной шкале от 0 до 3 баллов, составили группу с низким риском развития уролитиаза. Данной категории больных проведены клиничко-лабораторные исследования, а также ультразвуковая сонография МВС. Как правило, у детей данной группы отсутствуют клиничко-лабораторные и ультрасонографические проявления уролитиаза. Поэтому они наблюдаются в условиях поликлиники. Дети, набравшие от 4 до 6 баллов и вошедшие в группу среднего риска, также требуют проведения клиничко-лабораторных и инструментальных исследований. Пациентов, у которых обнаружены клинические и/или лабораторные, инструментальные изменения по уролитиазу, необходимо направить к детскому урологу в специализированную клинику для дальнейшего комплексного

обследования и лечения. В случае, когда результаты клинико-лабораторных и инструментальных методов исследования не выявляют признаков МКБ, рекомендуется проведение иммуногенетического анализа. Анализ проведённых исследований показал, что пациенты с высоким риском развития МКБ (от 7 до 10 баллов), требуют особого внимания. В случае выявления клинических признаков заболевания у детей, они направляются к детскому урологу специализированной клиники. В случае отсутствия клинических признаков уролитиаза, необходимо провести лабораторные и инструментальные исследования. Дети, у которых были выявлены соответствующие изменения в лабораторных анализах и в данных ультрасонографии МВС, должны быть направлены к детскому урологу в специализированную клинику. При отсутствии изменений в лабораторных анализах и данных УЗИ, проводится иммуногенетическое тестирование. Детям с высоким риском развития МКБ и при наличии полиморфизма генов возникает необходимость проведения комплекса мероприятий по предупреждению развития уролитиаза. В тех случаях, когда изменения на генном уровне не обнаруживаются, дети должны находиться под наблюдением врача в амбулаторно-поликлиническом учреждении.

Заключение. Разработанный алгоритм ранней диагностики и прогнозирования развития мочекаменной болезни у детей в условиях поликлиники позволит выявить группу риска с построением персонализированного подхода к маршрутизации пациента на этапах наблюдения.

Ключевые слова: уролитиаз у детей, прогнозирование, ранняя диагностика, генетический фактор, прелитиаз, алгоритм диагностики.

POLIKLINIKA SHAROITIDA BOLALARDA UROLITIAZNI BOSHQARISHGA SHAXSIYLASHTIRILGAN YONDASHUV

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Bugungi kunda urolitiyoz nafaqat tibbiy muammo, balki jiddiy ijtimoiy-iqtisodiy va demografik muammodir.

Maqsad. Poliklinika sharoitida bolalarda urolitiyozni bashorat qilish va erta tashxislash uchun ilmiy asoslangan algoritmni ishlab chiqish.

Materiallar va usullar. Tadqiqotda urolitiaz bilan kasallangan bolalar (n=100) - asosiy guruh, nisbatan sog'lom bolalar (n=100) - nazorat guruhi; va ularning ota-onalari. Ishlab chiqilgan anketadan foydalanib, onadagi homiladorlik jarayonini, ota-onalarning surunkali kasalliklari mavjudligini, shuningdek, tosh hosil qiluvchi moddalarning holatini, ya'ni qon va siydikning biokimyoviy tadqiqotlarini o'tkazishni hisobga olgan holda bolalar va ularning ota-onalarining hayot tarixini baholash uchun chuqur tahlil o'tkazildi.

Tadqiqot natijalari. Tadqiqot ishlari natijalariga ko'ra poliklinika sharoitida xavf omillari va immunogenetik moyillikni hisobga olgan holda bolalarda STKni erta tashxislash va rivojlanishini

bashorat qilish algoritmini ishlab chiqdik. Ushbu algoritm bolalarda urolitiazni xavf omillarini hisobga olgan holda preklinik bosqichda aniqlash uchun mo'ljallangan. Algoritmga ko'ra, birinchi harakat paytida anamnestic ma'lumotlarni hisobga olgan holda STK rivojlanish xavfi darajasini baholash kerak. Shu maqsadda 10 ta asosiy savol ishlab chiqilgan bo'lib, ular asosida 10 balli shkala bo'yicha xavf darajasini aniqlash mumkin. Ushbu algoritmning ikkinchi bosqichini bajarishda rivojlanish xavfi bo'lgan bolalarni yo'naltirish kerak. Shunday qilib, 10 balli shkala bo'yicha 0 dan 3 ballgacha ball to'plagan bolalar profilaktik tekshiruvlar taqvimiga ko'ra ambulatoriya sharoitida kuzatiladi. 4 dan 6 ballgacha to'plagan bolalarda chuqur klinik, laboratoriya va instrumental tekshiruvlar o'tkazilishi kerak. Shu bilan birga, hech qanday o'zgarishlar aniqlanmagan bolalar guruhida immunogenetik tadqiqotlar o'tkazish tavsiya etiladi: gen polimorfizmi aniqlanadi – urolitiaz rivojlanishining oldini olish choralari; aniqlanmasa – mos ravishda ambulatoriya sharoitida kuzatuv amalga oshiriladi. 7 dan 10 ballgacha to'plagan bolalar guruhiga alohida e'tibor qaratish lozim. Agar urolitiaz rivojlanish xavfi yuqori bo'lgan bolalarda klinik belgilar aniqlansa bola ixtisoslashgan klinikaning bolalar urologiga yuboriladi. Klinik belgilar bo'lmasa, laboratoriya va instrumental tadqiqotlar o'tkazish kerak. Agar testlarda o'zgarishlar bo'lmasa, immunogenetik tadqiqot o'tkaziladi. Urolitiaz rivojlanish xavfi yuqori bo'lgan va gen polimorfizmi mavjud bo'lgan bolalar uchun immunogenetik tadqiqot o'tkazishda urolitiaz rivojlanishining oldini olish choralari ko'rish zarur bo'ladi. Gen darajasida o'zgarishlar aniqlanmagan hollarda, bola ambulatoriyada shifokor nazorati ostida bo'lishi kerak.

Xulosa. Poliklinika sharoitida bolalarda urolitiazning rivojlanishini erta tashxislash va bashorat qilish uchun ishlab chiqilgan algoritm kuzatuv bosqichlarida bemorni yo'naltirishga shaxsiylashtirilgan yondashuvni qurish bilan xavf guruhini aniqlashga yordam beradi.

Kalit so'zlar: bolalardagi urolitiaz, bashorat qilish, erta tashxis, genetik omil, prelitiaz, diagnostika algoritmi.

Introduction

The incidence of urolithiasis in children is increasing worldwide. The incidence of urinary stone disease among all urological pathologies of childhood is 3%. It should be noted that the clinical course of the disease in children differs from that in adults. This causes a special interest and necessity to study epidemiological processes by sex and age categories, as well as regionally with determination of causal risk factors of urolithiasis occurrence. Taking into account these data it is possible to develop an algorithm for prediction and early diagnosis of the disease, which will lead to a decrease in morbidity and timely start of treatment measures that will allow to correct the determined disorders, prevent complications and the development of recurrences of stone formation.

Despite many population-based molecular genetic studies, molecular genetic markers of urolithiasis are still insufficiently studied. In this regard, it is relevant to study the association of genotypes of polymorphic markers of vitamin D receptor and osteopontin genes with urolithiasis in Uzbekistan.

Special attention in the world is paid to the study of various aspects of recurrence of urolithiasis [1, 2, 10]. A number of risk factors for recurrences of the disease have been identified, high-tech surgical methods of urinary stone removal, dietary therapy, conservative medication methods of correction of stone-forming substance metabolism disorders have been developed [3, 4, 5, 6, 11]. However, despite the obvious successes achieved in the treatment of patients with urolithiasis, the frequency of recurrence of uroliths remains considerable and according to various authors it can reach 40 - 70% [7, 8, 9, 14]. In connection with the above, the problem of recurrence of urolithiasis continues to be urgent.

Currently, a number of genetic studies aimed at finding associations of urolithiasis and its recurrences with polymorphic gene variants are carried out in many countries of the world. In connection with the above, at the first stage of our work we analysed polymorphisms of the following genes: VDR (Fok-I) and osteopontin (rs2853744).

Purpose of the study: To develop a scientifically based algorithm for prediction and early diagnosis of urolithiasis in children in primary health care.

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%).

Using the developed questionnaire, an in-depth analysis was carried out to assess the life history of children and their parents, taking into account the course of pregnancy in the mother, the presence of chronic diseases of the parents, as well as the status of stone-forming substances, i.e. biochemical studies of blood and urine.

Result and discussions

Using the developed questionnaire in the main group, an in-depth analysis was conducted to assess the life history of children and their parents. In the course of our study, the main group of children with urolithiasis was divided into two subgroups: subgroup A included 39 (39.0%) children whose parents were diagnosed with urinary stone diseases; subgroup B included 61 (61.0%) patients with urolithiasis whose parents had no clinical, laboratory and instrumental signs of urinary stone disease. The control group consisted of 100 (100%) children with parents in whom urolithiasis was excluded by anamnestic and clinical and laboratory investigations.

According to the data obtained from the questionnaire, it should be noted that 17.0% of the families of subgroups A and B lived in environmentally unfavourable conditions, with the largest number of technogenic enterprises, factories, and industrial facilities with emissions exceeding the maximum permissible concentration, which influenced the formation of anomalies of the urinary excretory system (UES) contributing to the development of urolithiasis. 10.3% of parents of subgroup A had work related to harmful industries (with chemical reagents), field work; about 5.1% of parents had bad habits, 10.3% had a sedentary lifestyle.

Questionnaire survey on the presence of chronic diseases among parents identified them among fathers in 16 (41.0%) cases and among mothers - 24 (61.5%). Analysis of the above-mentioned diseases among parents showed predominance of respiratory system diseases among mothers in 4 (10.3%), gastrointestinal tract diseases in 3 (7.7%), genital organs diseases in 2 (5.1%), nervous system diseases in 9 (23.1%), endocrine system diseases in 3 (7.7%), cardiovascular system diseases in 3 (7.7%). Whereas among male parents, chronic diseases of the respiratory, endocrine and cardiovascular systems were most often identified.

Heredity of urolithiasis in parents revealed its presence in: fathers - 19 (48.7%), mothers - 24 (61.5%), at that in 7 (17.9%) couples urolithiasis was determined in both parents. In subgroup A, 3 (7.7%) parents underwent surgery for urinary stone disease, others were characterised by the presence of small concretions in the kidneys, and 5 (12.8%) parents had permanent discharge of small concretions with the development of chronic pyelonephritis.

Analysis of the course of pregnancy in subgroup A indicated a complicated pregnancy with varying degrees of pre-eclampsia in 76.9% of mothers; 71.8% had anaemia; 25.6% had multiple pregnancy, threat of termination, and 59.0% had oedema and arterial hypertension. In subgroup B, these anamnestic parameters were detected in 70.5%, 59.0%, 18.0% and 16.4% of cases, respectively. In the control group, pregnancy complications were significantly lower. The Pearson χ^2 test showed a direct

correlation between the presence of chronic diseases, complicated pregnancy in mothers and the development of urinary stone disease in children of subgroups A and B ($\chi^2=10.12$; $p=0.0013$).

The study of the incidence of urolithiasis and the relationship of the disease with the intake of drugs by mothers during pregnancy showed a direct correlation between the use of antiviral, antibacterial, vitamins, dietary supplements and hypotensive, with $\chi^2=10.13$, $p=0.024$.

It is well known that such a risk factor as irrational nutrition is of great importance in the development of urolithiasis. The study of this factor showed that in subgroup A, the majority of children and their parents favoured vegetable food (46.3%) and protein food (34.4%), while the consumption of dairy and mixed food was 16.1% and 3.2%, respectively. Subgroup B favoured plant and protein food with 47.5% and 33.2%, dairy food with 15.5% and to a lesser extent mixed food with 3.8%. In the control group, mixed food prevailed - 61.0%, somewhat less frequently mixed with preference for dairy (27.0%) or protein (12.0%) food.

The study of drinking habits showed that more than half of the respondents in subgroups A and B - 52.0% had no information about the quality of the consumed liquid. Most of them - more than 63% - used natural water, while the remaining 37% used water from centralised water supply sources. At the same time, children using water from natural water bodies had a significant tendency and higher frequency of urolithiasis ($\chi^2=2.74$; $p=0.022$).

The analysis of water drinking regimen revealed that the risks of urolithiasis development increased when the volume of fluid intake decreased to less than 1-1.5 litres per day.

Currently, due to the development of immunogenetic studies, it has become possible to search for genetic markers that contribute to and take a direct part as risk factors for stone formation and subsequent development of urolithiasis. The revealed polymorphism of VDR and interleukin-1 β genes indicates a high risk of urolithiasis formation in children. The genetic markers of predisposition to urinary stone disease development in children are alleles ff+Fff of VDR gene and alleles C/C of interleukin-1 β gene. Therefore, these indicators can serve as immunogenetic criteria for predicting the development of urolithiasis in children at the preclinical stage of the disease.

Based on the results of the research work and to solve the problem, we have developed an algorithm for early diagnosis of urolithiasis in children at the preclinical stage of the disease in outpatient and polyclinic conditions, taking into account risk factors and immunogenetic predisposition.

For this purpose, 10 basic questions were developed, on the basis of which the degree of risk can be identified individually for each child on a 10-point scale. By summarising the results obtained, the risk of developing urolithiasis is predicted:

- 0 to 3 points - low risk of urolithiasis;
- 4 to 6 points - medium risk of urolithiasis;
- 7 to 10 points - high risk of urolithiasis.

When performing the second step of the developed algorithm, the patients are routed depending on their attribution to one or another degree of risk of urinary stone disease development.

Thus, children who scored 0 to 3 points according to a 10-point scale formed a group with a low risk of developing urolithiasis. This category of patients underwent clinical and laboratory investigations, as well as ultrasound sonography of the urinary system. As a rule, children in this group do not have clinical, laboratory and ultrasonographic manifestations of urolithiasis. Therefore, they are observed by a doctor in outpatient and polyclinic conditions according to the approved calendar of preventive examinations.

Children who scored from 4 to 6 points and entered the group of average risk, also require clinical, laboratory and instrumental studies. Patients found to have clinical and/or laboratory and instrumental changes in urolithiasis should be referred to a paediatric urologist in a specialised clinic for further comprehensive examination and treatment. If the results of clinical, laboratory and instrumental methods of investigation do not reveal signs of urolithiasis, immunogenetic analysis is recommended. If the results of testing for immunogenetic predictors do not indicate their polymorphism, the child should be under the supervision of a doctor in outpatient and polyclinic conditions. Detection of VDR and interleukin-1 β gene polymorphisms in this group of patients requires an appropriate set of measures to prevent the development of urolithiasis, including metaphylaxis.

Analyses of studies have shown that patients at high risk of developing urinary stone disease (7 to 10 points) require special attention. If clinical signs of the disease are detected in children, as a rule,

they are referred to a paediatric urologist of a specialised clinic. In the absence of clinical signs of urolithiasis, laboratory and instrumental investigations (ultrasound) should be performed. Children with relevant changes in laboratory tests and ultrasonography of the urinary tract should be referred to a paediatric urologist in a specialised clinic. In the absence of changes in laboratory tests and ultrasonography data, immunogenetic testing is performed. Children with a high risk of developing urolithiasis and in the presence of gene polymorphism there is a need for a set of measures to prevent the development of urinary stone disease. In cases where changes at the gene level are not detected, children should be under the supervision of a doctor in an outpatient clinic.

Conclusion

Thus, the developed algorithm for early diagnosis of urolithiasis in children and their subsequent routing according to the risk group (low, medium or high) will contribute to the detection of urinary stone disease at the preclinical stage in primary care.

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