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Tactics for treating young children with pyelonephritis and vesicoureteral reflux associated with impaired fibrillogenesis

Nataliia Lukyanenko[1,2] · Evelina Lenha[3] · Anastasiya Spaska[4,5] · Tetiana Klets[6] · Tetiana Shevchenko[6]

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Abstract

The purpose of this study is to substantiate the choice and evaluate the effectiveness of therapeutic tactics aimed at suppressing collagen formation and improving metabolic processes in the kidney parenchyma in young children with pyelonephritis against the background of vesicoureteral reflux associated with undifferentiated tissue dysfunction. 67 children from 2 weeks to 3 years old with pyelonephritis and vesicoureteral reflux were examined. All children during the period of remission of the inflammatory process were examined for the content of oxyproline in the urine. Urine crystallinity and urinary excretion were determined, and markers of the morphofunctional state of the cytomembranes of the renal epithelium were determined: calcification test—the presence of polar lipids in the urine and test for the presence of lipid peroxidation products in the urine. Children with high urinary hydroxyproline excretion prior to protocol treatment of pyelonephritis during the remission of the inflammatory process at the stage of maintenance therapy were recommended to receive metabolic preparations that can inhibit collagen formation and improve parenchyma metabolic processes during the month—vitamin E 10% and L-carnitine in age-related doses. After 6 months, a study was made on the functional state of the renal parenchyma in the dynamics of treatment. After metabolic antihypoxic and membrane-protective therapy, there was a significant positive dynamic of all markers of tissue hypoxia and membrane destruction in the kidney parenchyma, which confirms the inhibition of collagen formation processes and a decrease in tissue hypoxia with vitamin E and L-carnitine in age-related doses.

Keywords Metabolic therapy · Urine · Tissue hypoxia · Undifferentiated dysplasia · Renal epithelial

Introduction

Over the past decade, the prevalence of diseases of the urinary system among young children in Ukraine has not decreased, despite the successes achieved in the development of methods for their diagnosis and treatment. The frequency of their atypical progradient low-symptom course is increasing. Every year, the frequency of congenital malformations of the urinary system increases. Malformations of the urinary system make up from 26.0 to 35.0% of all cases of congenital malformations [1]. In this regard, scientists are considering the possible causes of such a situation and hypotheses are put forward on the totality of adverse exogenous and endogenous factors that implement the "program" of the disease at all levels of the body, starting with the cellular one. It can be said that a feature of young children is the high plasticity of the urinary system, which, with early diagnosis and timely correction of the defect, helps prevent the development and progression of irreversible consequences [2]. During practical work, family doctors and pediatricians

✉ Nataliia Lukyanenko
NSLukyanenko@gmail.com

1 Department of Clinical Genetics, Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine, 31a M. Lysenko Str., Lviv 79008, Ukraine

2 Department of Propaedeutics of Pediatrics and Medical Genetics, Danylo Halytsky Lviv National Medical University, 69 Pekarska Str., Lviv 79010, Ukraine

3 Department of Bioorganic and Biological Chemistry and Clinical Biochemistry, Bukovinian State Medical University, 2 Teatralnaya Sq., Chernivtsi 58002, Ukraine

4 College of Medicine, Ajman University, University Str., Al-Jurf, Ajman, United Arab Emirates

5 Center of Medical and Bio-allied Health Sciences Research, Ajman University, University Str., Al-Jurf, Ajman, United Arab Emirates

6 Department of Pediatrics No. 4, Bogomolets National Medical University, 13 Taras Shevchenko Blvd., Kyiv 01601, Ukraine

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are more likely to encounter manifestations of undifferentiated connective tissue dysplasia. Compared with connective tissue diseases, which are based on gene defects with a certain type of inheritance, undifferentiated connective tissue dysplasia is characterized by multifactorial genesis and polymorphism of the clinical picture [3]. Genetic defects in the synthesis of collagen lead to a decrease in the number of its transverse bonds and an increase in the number of readily soluble fractions, which is hydroxyproline. It is considered the main biochemical marker for the presence of undifferentiated connective tissue dysplasia [4].

At the same time, one of the leading pathogenetic factors in impaired renal function is hypoxia, caused by both hemodynamic and tissue respiration disorders in this pathology, and is one of the factors of impaired connective tissue metabolism [5]. It is known that oxalate-calcium crystalluria is a marker of tissue hypoxia of the parenchyma and membrane-pathological state of the kidneys [6, 7]. Indicators that directly depend on the amount of adenosine triphosphoric acid (ATP) in the cells of the renal epithelium include tests for the anticrystalline ability of urine that characterize both the presence of tissue hypoxia and the stability of the cytomembranes of the renal epithelium; therefore they also include the degree of hypoxia renal parenchyma [8]. The main mechanism for the implementation of tissue hypoxia at the cellular level is the activation of non-enzymatic lipid peroxidation [9]. Despite the ongoing study of this problem in older children, there is a need for the early diagnosis of undifferentiated connective tissue dysplasia in children and infants with manifestations of the pathology of the urinary system. Early detection of this pathology may provide the possibility of correcting connective tissue dysfunction and will positively affect the effectiveness of treatment and allow slowing down further development of the disease.

With connective tissue dysplasia, there is a decrease in redox processes in the mitochondria and L-carnitine deficiency. Carnitine is an essential vitamin-like substance [10]. The main metabolic functions of carnitine are associated with the processes of conversion of biological energy, which plays an important role in cellular metabolism and, above all, in energy metabolism. Therefore, in especially large quantities it is found in tissues that require high energy supply—the kidneys, skeletal muscles, myocardium of the heart, brain, and liver. Carnitine provides the transfer of fatty acids through cell membranes from the cytoplasm to mitochondria, where they are oxidized and acetyl Coenzyme A is released—a substrate for the Krebs cycle with the formation of a large amount of metabolic energy (in the form of ATP) [11]. It is known that antioxidants protect cells, including fibroblasts, which are responsible for the reproduction of connective tissue, from the negative effects of free radicals in the center of the cell [12].

Based on the foregoing, the goal of the study was formulated. The objective of the study is to substantiate the choice and evaluate the effectiveness of treatment tactics aimed at improving metabolic processes in the renal parenchyma and reducing collagen formation in young children with pyelonephritis against the background of vesicoureteral reflux associated with undifferentiated connective tissue dysplasia.

Materials and methods

The study included 67 children with pyelonephritis and vesicoureteral reflux, aged 1 month to 3 years. Diagnosis of pyelonephritis and vesicoureteral reflux was verified according to examination and treatment protocols in pediatric urology and pediatrics [13, 14]. The control observation group included 65 young children with acute pyelonephritis, who did not reveal any congenital malformations of the urinary system after examination, including vesicoureteral reflux and phenotypic signs of undifferentiated connective tissue dysplasia. The second control group consisted of 40 somatically healthy children of the same age. In order to diagnose the presence of undifferentiated connective tissue dysplasia for all children in the period of remission of the inflammatory process, a test was performed for the content of oxyproline in the urine [15]. The following markers of tissue hypoxia of the parenchyma were determined: a test for anticrystalline ability of urine and daily excretion of salts in urine according to the method of Veltishcheva and Yurieva [16].

Markers of the morphofunctional state of the cytomembranes of the renal epithelium were studied: a calcification test—the presence of polar lipids in the urine and a test for the presence of lipid peroxidation products in the urine according to the method of Yurieva [16]. For young children with vesicoureteral reflux and undifferentiated dysplasia of the connective tissue, in whom the urine was found to have high excretion of oxyproline, during the period of remission of the inflammatory process at the stage of maintenance therapy, it was recommended to take medications for a month that can reduce collagen formation and improve metabolic processes in the parenchyma kidneys—vitamin E 10% and L-carnitine in age doses, that is, metabolic therapy. In order to compare the treatment results, the data of children with vesicoureteral reflux and undifferentiated dysplasia of the connective tissue after treatment using metabolic agents were compared with the data of children who did not receive them. Children, in accordance with this, were divided into two subgroups. 6 months after the first examination, the functional state of the kidney parenchyma was studied in the dynamics of treatment.

One of the most common congenital malformations of the urinary system in young children is vesicoureteral reflux, which is observed in 1.0–2.0% of the pediatric population.

Its frequency in children with infections of the urinary system reaches 70.0%, which is caused by a violation of the closing mechanism of the bladder-ureteric segment of the urinary tract, as a result of which a certain amount of urine transported through the ureter to the urinary bladder constantly or periodically returns to the upper urinary tract in the direction kidneys [17, 18]. Today, there are more and more reports in literature that one of the causes of the formation of congenital malformations is microanomalies of the internal organs, which, in turn, are a manifestation of connective tissue dysplasia and lead to the attachment of an** infectious inflammatory; in this case the pathology has a permanent course of the process with the possibility of further chronization [19]. The spread of connective tissue dysplasia, which can be either differentiated or undifferentiated, is 35.0–64.0%, and therefore this pathology has acquired the importance of an urgent medical problem [3].

Results and discussion

The study took place in two stages. At the first stage, clinical and ultrasound examinations of children were carried out with an emphasis on the most frequent clinical, morphofunctional, and visceral disorders characteristic of undifferentiated connective tissue dysplasia. They are recommended for accounting Kadurina with additional criteria Milkovsky-Dimitrov and Karkasheva [19]. The results of clinical and ultrasound examinations of children with vesicoureteral reflux are given in Table 1. The data obtained indicate that in children with vesicoureteral reflux in comparison with the data of children in the control group, phenotypic and clinical signs of undifferentiated connective tissue dysplasia were diagnosed significantly more often: In particular, deviations in physical development—in 20.89% of the examined, skeletal anomalies—in 14.9%, on the part of the skin and nervous system—in 11.9% of children, and on the part of the muscular system—in 16.4% of children. Such a significant frequency of phenotypic signs of undifferentiated dysplasia of the connective tissue in the examined children required a study of the content of hydroxyproline in the urine to confirm the presence of connective tissue dysfunction. Therefore, the second stage of the study was the determination of the main biochemical marker of undifferentiated connective tissue dysplasia syndrome among children with vesicoureteral reflux—the content of oxyproline in daily urine.

In order to compare the results of examination of patients with pathology of the urinary system and undifferentiated dysplasia of the connective tissue, data of children, who do not have such an association, were divided into two groups according to the presence or absence of oxyproline in the urine (Oxyproline "positive" and Oxyproline "negative"). Thus, a positive urinary hydroxyproline test was diagnosed in 61.8% of children with vesicoureteral reflux, that is, more than half. At the same time, in children with pyelonephritis without vesicoureteral reflux, hydroxyproline was detected only in 21.5% of the examined children (Table 2).

Considering the obtained data, it seemed appropriate to clarify the state of renal parenchyma in young children with vesicoureteral reflux against the background of detected phenotypic and clinical signs of undifferentiated connective tissue dysplasia—to determine the indicators of tissue hypoxia of the parenchyma and the state of renal epithelial cytomembranes in both subgroups of children

Table 1 Analysis of phenotypic signs of undifferentiated connective tissue dysplasia in young children with vesicoureteral reflux and control groups

Body systems	Groups of children					
	With vesicoureteral reflux, $N=67$		Without vesicoureteral reflux, $N=65$		Healthy, $N=40$	
	n	%	*n*	%	*n*	%
Physical decline	14	20.89*	7	10.8*	2	5.0
Skin (soft, increased elasticity)	8	11.9*	4	6.2	3	7.5
Nails (fragile, with patches of focal aplasia)	3	4.5*	1	1.5*	–	–
Hair (thin, dull)	1	1.5*	–	–	–	–
Auricles (soft, sagging lobe, enlarged)	–	–	–	–	–	–
Muscular system (diastasis of the muscles of the abdominal wall, their hypotension)	11	16.4*	5	7.6*	1	2.5
Skeletal abnormalities (various bone-cartilaginous dysplasias, flat feet)	10	14.9*	3	4.6*	1	2.5
Nervous system (myatonic syndrome)	8	11.9*	3	4.6*	–	–
Cardiovascular system (valve prolapse, false chords)	2	2.9	1	1.5	1	2.5
Gastrointestinal tract (biliary dyskinesia, functional and anatomical defects of the gallbladder)	6	8.9*	5	7.6*	1	2.5

*Significant difference between the data of children with pyelonephritis and healthy

Table 2 Distribution of examined children with vesicoureteral reflux and control groups by the presence of oxyproline in daily urine

Indicator	Children group					
	With vesicoureteral reflux, $N=67$		Without vesicoureteral reflux, $N=65$		Health, $N=40$	
	n	%	*n*	%	*n*	%
Oxyproline "positive"	38	61.8*	14	21.5*	2	5.0
Oxyproline "negative"	29	38.2*	51	78.5*	38	95.0

*Significant difference between the data of children with pyelonephritis and healthy, $p<0.01$

Table 3 Indicators of tissue hypoxia of the renal parenchyma and membrane destruction in children with vesicoureteral reflux on the background of undifferentiated connective tissue dysplasia and control groups, ($M \pm m$)

Indicator	Children group					
	With vesicoureteral reflux, $N=67$		Without vesicoureteral reflux, $N=65$		Healthy, $N=40$	
	Oxyproline (+), $n=38$	Oxyproline (−), $n=29$	Oxyproline (+), $n=14$	Oxyproline (−), $n=51$	Oxyproline (+), $n=2$	Oxyproline (−), $n=38$
Anticrystalline ability of urine to calcium oxalates, conv. units						
$M \pm m$	0.17 ± 0.04**	0.11 ± 0.02**	0.13 ± 0.03	0.11 ± 0.02	0.08 ± 0.03	0.08 ± 0.03
q	1.0	1.0	1.0	0.9	0.1	0.1
The anticrystalline ability of urine to calcium phosphate						
$M \pm m$	0.11 ± 0.04**	0.09 ± 0.03**	0.12 ± 0.03	0.10 ± 0.03	0.05 ± 0.01	0.05 ± 0.01
q	0.90**	0.80**	0.86	0.84	0.1	0.1
Antcrystalline ability of urine to Tripel-phosphates, conv. units						
$M \pm m$	0.16 ± 0.03**	0.12 ± 0.02**	0.11 ± 0.02	0.09 ± 0.02	0.02 ± 0.01	0.02 ± 0.01
q	1.0**	1.0**	1.0	1.0	0.05	0.05
Daily excretion of calcium oxalates, mol/day						
$M \pm m$	37.87 ± 4.3*·**	31.5 ± 10.14*·**	17.87 ± 4.5	16.75 ± 5.6	19.5 ± 0.03	19.5 ± 0.03
q	0.72*·**	0.60*·**	0.45	0.39	0.15	0.15
Daily excretion of calcium phosphate, mol/day						
$M \pm m$	3.9 ± 0.15*·***	6.24 ± 0.7*	9.8 ± 0.15	10.6 ± 0.61	11.5 ± 0.04	11.5 ± 0.04
q	0.58*	0.33*	1.0	0.9	0.08	0.08
Daily urinary excretion, mmol/day						
$M \pm m$	2.54 ± 0.25***	5.03 ± 2.3*·***	1.64 ± 0.35	2.05 ± 0.86	4.5 ± 0.01	4.5 ± 0.01
q	0.58*	0.47*	0.53	0.45	0.1	0.1
Urinary lipid peroxidation products excretion, g/day						
$M \pm m$	0.36 ± 0.05*·**	0.27 ± 0.04*·**	0.82 ± 0.17**	0.71 ± 0.16**	0.09 ± 0.01	0.09 ± 0.01
q	1.0	0.89	0.74	0.69	0.10	0.10
The frequency of determination of polar lipids in the urine, (q)						
Negative	0.18*·**·***	0.35*·***	0.50	0.50	0.87	0.87
Positive	0.82*·**·***	0.65*·**·***	0.50*	0.50*	0.13	0.13

*Significant difference between the data of children with vesicoureteral reflux and a group of children with acute pyelonephritis without reflux; $p_1<0.01$; **Significant difference between the data of children with vesicoureteral reflux and the control group of healthy children, $p_2<0.01$; ***Probable difference of the indicator between the data of children with oxyproline (+) and oxyproline (−); $p_3<0.001$

(Table 3). Studies were conducted during the period of clinical and laboratory remission of the inflammatory process. In all examined children, with vesicoureteral reflux and pyelonephritis without anatomical abnormalities, the anticrystalline ability of urine was significantly reduced in comparison with the data of healthy children, although the average values did not differ from each other. This indicates the presence of tissue hypoxia and destruction of the cytomembranes of the renal epithelium of children (Table 3) with pyelonephritis even in the period of clinical and laboratory remission. When comparing the data of children with positive and negative samples for oxyproline, a decrease in the anticrystalline ability of urine was observed in children with increased excretion

of oxyproline with urine, which was observed in the vast majority of children with vesicoureteral reflux. This was especially true of the anticrystalline ability of urine to calcium oxalates, which indicates an oxygen deficiency in the kidney parenchyma in children with impaired collagen formation against the background of congenital malformations.

The daily excretion of oxalates in the examined children with vesicoureteral reflux and children with acute pyelonephritis without reflux, both in average values and in frequency, significantly doubled and significantly differed from these healthy children, which indicates pronounced processes of tissue hypoxia and membrane destruction (Table 3) in children of the first group. In 58% of children with vesicoureteral reflux, in whom signs of undifferentiated dysplasia of the connective tissue were found, the excretion of calcium phosphate with daily urine was significantly reduced. This indicates the presence of hypophosphaturia as a marker of tissue hypoxia and tubular dysfunction of the renal parenchyma epithelium and requires correction of the revealed disorders. Considering the absence of dysmetabolic nephropathy in the examined children, it can be concluded that indicators of the anticrystalline ability of urine and daily excretion of salts with urine make it possible to establish the presence of tissue hypoxia and membrane pathological processes from the renal epithelium and renal parenchyma at an early preclinical stage. The total reaction products of lipid peroxidation in the urine were observed in all examined children with vesicoureteral reflux, in two-thirds of children with pyelonephritis without reflux, and 10.0% of healthy children (Table 3).

The highest level of lipid peroxidation products in urine is 0.82 ± 0.17 conv. units observed in sick children with acute pyelonephritis. This is consistent with the literature, according to which the lipid peroxidation reaction is a nonspecific reaction of the body in acute inflammatory conditions. In children with vesicoureteral reflux and patients with acute pyelonephritis, in whom increased excretion of oxyproline with urine was observed, lipid peroxidation processes were more pronounced when compared with data from children in whom such excretion was not observed. This may indicate a decrease in reactive oxygen species and energy deficiency in the parenchyma, namely in children with a positive test for hydroxyproline. The appearance in the daily urine of polar lipids was observed in 82.0% of the examined children with a positive reaction to oxyproline against the background of vesicoureteral reflux, which was almost twice as much as in child with acute pyelonephritis (50.0%) and significantly differed from the data healthy children (13.0%). This indicates a significant increase in membrane destruction processes in children with impaired fibrillogenesis, which creates the conditions for the progression of the pathological process in kidney tissue in children with vesicoureteral reflux and undifferentiated connective tissue dysplasia (Table 3).

Thus, a search is required for methods of correcting the revealed changes in accordance with the presence of enhanced collagen formation, tissue hypoxia, and membranolysis. To protocol treatment of pyelonephritis in children with high excretion of oxyproline in the urine, metabolic therapy was added: vitamin E 10% and L-carnitine (Agvantar) in age doses for a month. The results of renal parenchyma in the follow-up of treatment were compared with the data of children who received only protocol treatment. The results are shown in Table 4. The anticrystalline ability of urine to calcium phosphates in intensity and frequency decreased more effectively in children with vesicoureteral reflux on the background of undifferentiated connective tissue dysplasia, to which metabolic therapy was added to protocol treatment (Table 4). At the same time, in children with increased excretion of oxyproline in the urine, the frequency of decrease in the urinary anticrystalline capacity decreased significantly. This indicates a positive effect of metabolic therapy aimed at reducing tissue hypoxia and membrane protection in children who did not have developmental abnormalities. After metabolic therapy, in children with vesicoureteral reflux, urinary phosphate excretion tended to increase (from 3.9 ± 0.15 to 8.9 ± 2.3 mol/day), and in a third of the children were examined urate excretion ($q = 0.49$ versus $q = 0.41$) (Table 4).

This indicates the effectiveness of antihypoxic and membrane-protective therapy and the functional capabilities of the renal parenchyma in children with vesicoureteral reflux on the background of undifferentiated connective tissue dysplasia [20, 21]. 2/3 of the examined children showed a pronounced positive dynamics of phosphate excretion in children with pyelonephritis without vesicoureteral reflux, in whom phosphate excretion was observed during the treatment. This proves the effectiveness of the therapy in children with pyelonephritis without kidney abnormalities and indicates the significance of precisely the abnormalities of the urinary system in resistance to the therapy of the revealed changes. In the dynamics of treatment of pyelonephritis with vesicoureteral reflux against the background of undifferentiated dysplasia of connective tissue in half of the children examined, lipid peroxidation products in daily urine continued to be detected. However, at the same time, in children with pyelonephritis without vesicoureteral reflux, the excretion of lipid peroxidation products significantly decreased, both in intensity and frequency of manifestation. However, when comparing the effectiveness of both treatment regimens, it turned out that children who received metabolic therapy showed better results, in contrast to children who received only protocol treatment (Table 4). A study of the excretion of polar lipids with daily urine in the treatment dynamics showed that, despite the positive clinical dynamics

Table 4 Indicators of tissue hypoxia of the renal parenchyma and membrane destruction in children with vesicoureteral reflux on the background of undifferentiated connective tissue dysplasia and control groups in the treatment dynamics, ($M \pm m$)

Indicator	Children group			
	With vesicoureteral reflux, $N=38$		Without vesicoureteral reflux, $N=14$	
	After metabolic therapy, $n=20$	Without metabolic therapy, $n=18$	After metabolic therapy, $n=8$	Without metabolic therapy, $n=6$
Anticrystalline ability of urine to calcium oxalates, conv. units				
Before treatment				
$M \pm m$	0.17 ± 0.04	0.17 ± 0.04	0.13 ± 0.03**	0.13 ± 0.03**
q	1.0	1.0	1.0	1.0
After treatment				
$M \pm m$	0.24 ± 0.08	0.28 ± 0.09	0.15 ± 0.03	0.18 ± 0.03
q	1.0	1.0	0.60	0.71
Anticrystalline ability of urine to calcium phosphates, conv. units				
Before treatment				
$M \pm m$	0.11 ± 0.04	0.11 ± 0.04	0.12 ± 0.03**	0.12 ± 0.03**
q	0.90	0.90	0.86	0.86
After treatment				
$M \pm m$	0.04 ± 0.02***	0.10 ± 0.02***	0.12 ± 0.05	0.14 ± 0.05
q	0.79	0.82	0.50	0.55
Urine anticrystalline ability to Tripelfos-veils, conv. units				
Before treatment				
$M \pm m$	0.16 ± 0.03	0.16 ± 0.03	0.11 ± 0.02**	0.11 ± 0.02**
q	1.0	1.0	1.0	1.0
After treatment				
$M \pm m$	0.17 ± 0.04	0.20 ± 0.05	0.13 ± 0.01	0.16 ± 0.01
q	1.0	1.0	0.60	0.66
Daily excretion of calcium oxalates, mol/day				
Before treatment				
$M \pm m$	37.87 ± 4.3*,**	37.87 ± 4.3*,**	17.87 ± 4.5	17.87 ± 4.5
q	0.72*,**	0.72*,**	0.45	0.45
After treatment				
$M \pm m$	30.26 ± 5.9	35.58 ± 6.3	17.8 ± 6.21	18.3 ± 6.96
q	0.84	0.91	0.37	0.44
Daily excretion of calcium phosphate, mol/day				
Before treatment				
$M \pm m$	3.9 ± 0.15*,**	3.9 ± 0.15*,**	9.8 ± 0.15	9.8 ± 0.15
q	0.58*,**	0.58*,**	1.0	1.0
After treatment				
$M \pm m$	8.9 ± 2.3	7.4 ± 2.8	7.68 ± 1.03	6.9 ± 1.39
q	0.49	0.41	0.35	0.3
Daily excretion of urate, mmol/day				
Before treatment				
$M \pm m$	2.54 ± 0.25	2.54 ± 0.25	1.64 ± 0.35	1.64 ± 0.35
q	0.58*	0.58*	0.53	0.53
After treatment				
$M \pm m$	2.08 ± 0.42	1.56 ± 0.94	3.15 ± 1.06	2.1 ± 1.59
q	0.49	0.41	0.33	0.28
Excretion of lipid peroxidation products in urine, g/day				
Before treatment				

Table 4 (continued)

Indicator	Children group			
	With vesicoureteral reflux, $N=38$		Without vesicoureteral reflux, $N=14$	
	After metabolic therapy, $n=20$	Without metabolic therapy, $n=18$	After metabolic therapy, $n=8$	Without metabolic therapy, $n=6$
$M \pm m$	0.36 ± 0.05*,**	0.36 ± 0.05*,**	0.82 ± 0.17**	0.82 ± 0.17**
q	1.0	1.0	0.50	0.50
After treatment				
$M \pm m$	0.30 ± 0.07*,**	0.34 ± 0.08*,**	0.06 ± 0.04***	0.34 ± 0.09***
q	1.0	1.0	0.37	0.42
The frequency of determination of polar lipids in the urine, q				
Before treatment				
"–"	0.18*	0.18*	0.50**	0.50**
"+"	0.82*,**	0.82*,**	0.50*	0.50*
After treatment				
"–"	0.44***	0.32	0.50	0.46
"+"	0.56	0.68	0.50	0.54

*Significant difference between the data of children with vesicoureteral reflux; **Probable difference between the data of children with vesicoureteral reflux and the control group of healthy children, $p_1 < 0.01$; ***Probable difference between the data of children with vesicoureteral reflux before and after treatment, $p_2 < 0.01$

and remission of the inflammatory process of the kidneys, in 56% of children with vesicoureteral reflux, 6 months after the first examination, some childrens' urine were still found to contain polar lipids. But in children with pyelonephritis and vesicoureteral reflux on the background of undifferentiated dysplasia of the connective tissue, who were additionally receiving metabolic therapy, there were significantly better results in comparison with the data of children who did not receive it ($q = 0.44$ versus $q = 0.32$) (Table 4).

Conclusions

The high frequency of detecting phenotypic signs of undifferentiated dysplasia of connective tissue and oxyproline in the urine of children with pyelonephritis against the background of vesicoureteral reflux reliably indicates the presence of disorders of fibrillogenesis in these children and, as a result, undifferentiated dysplasia of connective tissue. In young children with pyelonephritis against the background of vesicoureteral reflux, the presence of tissue hypoxia of the renal parenchyma and membrane destruction of the nephrothelium was revealed. In children with an association of the pathological process with undifferentiated dysplasia of the connective tissue, these changes were more pronounced. This is indicated by a more pronounced the excretion of oxalates and a decrease in the excretion of phosphates and urates with daily urine. This was accompanied by a significant intensification of lipid peroxidation processes and the appearance of polar lipids in daily urine.

After metabolic therapy and correction of collagen formation processes, there was a significant positive dynamic of all markers of tissue hypoxia and membrane destruction in the parenchyma of the kidneys of young children, antihypoxant and membrane-protective therapy were added to protocol treatment, which confirms the possibility of slowing down collagen formation processes and reducing tissue hypoxia when using vitamin E and L-carnitine in age doses for a month. Prospects for the further development of research are required in this direction: a molecular genetic study of markers of undifferentiated connective tissue dysplasia in young children with a vesicoureteral reflex in order to clarify the genetic determinant in the formation of undifferentiated connective tissue dysplasia is planned.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest All authors state they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A study was approved by National Ethics Commission of the Ministry of Health of the Ukraine.

Consent to participate The parents of all study participants gave written consent to participate.

References

1. Kryganova TA, Dlin VV (2016) The frequency of anomalies of the urinary system and the functional state of the kidneys, depending on the severity of connective tissue dysplasia in children. Russ Bull Perinatol Pediatr 3:81–86
2. Povshedna TYu, Shevchuk DV, Korniychuk NM (2015) The role of timely treatment of congenital malformations of the urinary system in the prevention of chronic renal failure in children. Biol Res 1:423–429
3. Semyanchuk VB (2015) Prevalence of manifestations of undifferentiated connective tissue dysplasia in children of Prykarpattia, patients with bronchial asthma. Act Prob Mod Med 15(2):149–154
4. Lukina TS (2015) Evaluation of the oxyproline marker and its value in women with undifferentiated connective tissue dysplasia. Mod Med Top Issues 6–7(41):6–10
5. Maydannyk VH, Burlaka YeA (2015) The state of metabolic-hypoxic disorders in diabetic nephropathy in children. Exp Clin Physiol Biochem 4:47–55
6. Averyanova NI, Balueva LG (2012) Oxalate crystalluria in children. Int J Appl Fund Res 5:25–27
7. Kens KA (2012) Non-invasive markers of renal dysfunction in young children with vesicoureteral reflux in the dynamics of surgical and metabolic treatment. Institute of Urology of the National Academy of Medical Sciences of Ukraine, Kyiv
8. Lukyanova LD (2013) Signal role of mitochondria in adaptation to hypoxia. Physiol J 59(6):141–154
9. Topchiy II, Kyryenko AN, Bondar TN, Lesovaya AV, Shchenyavskaya EN (2012) Lipid peroxidation and nitric oxide metabolism in patients with chronic kidney disease in the dynamics of treatment. Ukrainian J Nephrol Dial 1:3–8
10. Gubergrits NB, Golubova OA, Lukashevich GM (2012) L-Carnitine: from biochemical properties to clinical use. Mod Gastroenterol 2:114–121
11. Butolin EG, Chernyshova TE, Ivanova IL, Malkova AA, Pelin AI, Soloviev AA, Ovchinnikova EI, Shklyaeva LA (2012) Neurological aspects of connective tissue dysplasia: diagnosis, treatment, rehabilitation. Izhevsk State Medical Academy of Roszdrav, Izhevsk
12. Nagornaya NV, Chetverik NA (2010) Oxidative stress: impact on the human body, assessment methods. Child Health 2:140–145
13. Order of the Ministry of Health of Ukraine No. 627 "On approval of the protocol for the treatment of children with urinary tract infections and tubolointerstitial nephritis" (2008). https://zakon.rada.gov.ua/rada/show/v0627282-08#Text
14. Order of the Ministry of Health of Ukraine No. 140 "On amendments to the order of the Ministry of Health of Ukraine" (2008). https://zakon.rada.gov.ua/rada/show/v0140282-08#Text
15. Nyankovskyy SL, Dobryk OO, Iskiv MYu (2014) Patent No. 95526 "Method for diagnosing connective tissue dysplasia." Danylo Halytsky Lviv National Medical University, Lviv
16. Lukianenko NS, Hnateyko OZ, Kech NR, Pechenyk SO, Chaykovska HS, Kovaliv IB, Vishtak NV (2012) Algorithm for diagnosis and medical and genetic counseling of ecologically determined pathology in children living permanently in conditions of high concentrations of heavy metal salts and fluorine. National Academy of Medical Sciences of Ukraine, Kyiv
17. Nikitina NA, Starets YeA, Kalashnikova YeA, Galich SR, Sochinskaya TV (2013) Congenital anomalies in the number of kidneys: frequency, etiopathogenesis, prenatal diagnosis, clinical picture, physical development, diagnosis, treatment, prevention (part 1). Child Health 6(49):107–111
18. Kryganova TA, Aksenova MYe, Dlin VV (2016) Vesicoureteral reflux and its complications in children depending on the severity of connective tissue dysplasia. Russ Bull Perinatol Pediatr 4:93–97
19. Martynov AI, Nechayeva GI, Akatova YeV, Vershinina MV, Viktorova IA, Gromova OA, Drokina OV, Druk IV, Dubiley GS, Ilinykh AA, Kudinova YeG, Lisichenko OV, Loginova YeN, Lyalyukova YeA, Nagayeva TA, Nadey YeV, Plotnikova OV, Ponomareva DA (2016) National recommendations of the Russian scientific medical society of physicians for the diagnosis, treatment and rehabilitation of patients with connective tissue dysplasia. Med Bull North Cauc 1:2–76
20. Molcan J, Dobrovanov A, Koren R, Kralinsky K, Balaz V (2021) Unilateral scrotal hernia with dual ureter herniation: The first experience of successful surgical correction. Pediat - Zh im G.N. Speranskogo 100(4):171–75
21. Dobrovanov O, Kralinsky K, Molcan J, Kovalchuk VP (2019) Relevance of ultrasound neonatal screening of the urinary system. Ross Vest Perinatol i Ped 64(2):68–72. https://doi.org/10.21508/1027-4065-2019-64-3-68-72