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COURSE FEATURES OF PEDIATRIC RENAL MICROLITHIASIS AND OXIDATIVE STRESS IN CHILDREN

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Oxidative stress plays a major role in the development of metabolic renal diseases in children. We established the pediatric renal microlithiasis course in the setting of disorders of lipid peroxidation. 176 children aged 1 to 18 years were examined who were diagnosed with renal microlithiasis and were out-patients and in-patients in the Regional Children Counselling Outpatient Clinic and Nephrology Department of the Public Nonprofit Enterprise "Ivano-Frankivsk Regional Children`s Clinical Hospital of Ivano-Frankivsk Oblast Council" during the period of 2016 till 2019. Most commonly, in children the diagnosis of oxaluria (34.1 %) and oxalate-calcium nephropathy (30.1 %) was verified. Based on gender, girls prevail over boys (75.0 % and 25.0 %, $p<0.05$). It is established that pediatric renal microlithiasis occurs more commonly at the age of 13–17 years. The increase of primary lipid peroxidation product activity (diene conjugates) in the blood of sick children is evidence of activation of free radical processes in renal microlithiasis. The average rate of nitrites is significantly lower in children aged 13–17 years with phosphaturia (37.11 and 41.30 μmol/L, $p <0.01$). In elder children this index does not change compared to norm.

Key words: disease progression, children, nephrolithiasis, kidney calculi, oxidative stress, diagnosis.

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ОСОБЛИВОСТІ ПЕРЕБІГУ МІКРОНЕФРОЛІТІАЗУ ТА ОКСИДАНТНОГО СТРЕСУ У ДІТЕЙ

Оксидантний стрес відіграє провідну роль у генезі обмінної патології нирок у дитячому віці. Мета роботи: дослідити перебіг мікронефролітіазу у дітей, на тлі порушень ліпопероксидації. Обстежено 176 дітей, віком від 1 до 18 років, із мікронефролітіазом, які перебували на амбулаторному та стаціонарному лікуванні в обласній дитячій консультативній поліклініці та нефрологічному відділенні КНП «Івано-Франківська ОДКЛ ІФ ОР» м.Івано-Франківська, впродовж 2016–2019-го років. Найчастіше у дітей верифіковано діагноз оксалатурії (34,1 %) та оксалатно-кальцієвої нефропатії (30,1 %). За статтю дівчатка переважають хлопчиків (75,0 % і 25,0 %, $p<0,05$). Встановлено, що частіше мікронефролітіаз трапляється у віці 13–17 років. Підвищення активності первинних продуктів ліпопероксидації (дієнових кон'югат) в крові хворих дітей свідчить про активацію вільнорадикальних процесів при мікронефролітіазі. Найсуттєвіше ці показники зростали при уратурії, в меншій мірі - при оксалурії. Натомість, зниження рівня вторинних (ТБК-активних) продуктів перекисного окислення ліпідів свідчить про досі ефективну роботу антиоксидантного захисту в дітей шкільного віку, хворих на мікронефролітіаз. Середній рівень нітриту є значно нижчим у дітей віком 13–17 років із фосфатурією (37,11 та 41,30 мкмоль/л, $p<0,01$). У старших дітей цей показник не змінюється порівняно з нормою.

Ключові слова: клінічний перебіг, діти, мікронефролітіаз, ниркові камені, оксидантний стрес, діагностика.

The study is a fragment of the research project "Health state and features of adaptation in children in the Prykarpattya region with somatic disease, and its prevention", state registration No. 0121U111129.

As it is known, pediatric renal microlithiasis (dysmetabolic nephropathies, microurolithiasis, kidney calculi) belong to the group of diseases or, in keeping with other authors, premorbid conditions that are characterized by disorders of major metabolism types at all levels from the cellular to systemic one [4, 10, 15]. Incidence of this pathological condition within kidney morbidity during the last decades reached the level of 27–60 % of cases and does not show any tendency to decline [2, 4, 12]. Literature analysis of the last years is evident of the leading role of oxidative stress in the origin and progression of the micronephrolithiasis course in children [1, 8, 9]. Particular scientists indicate that staghorn calculi in nephrolithiasis can lead to profound shift of free radical balance [2, 6, 9]. Other scientists claim that the most significant disorders of metabolic homeostasis occur in patients with oxalate urolithiasis [1, 9]. This involves an elevation of malondialdehyde (MDA) and glutathione S-transferase in the setting of a decrease of catalase, superoxide dismutase and glutathione reductase profiles; also, this refers to general reduction of glutathione in all biological substrates in micronephrolithiasis. These changes are associated, on the other hand, with high content of oxalate and low level of citrate in the urine in patients with metabolic kidney disease [1, 2, 6]. Aside from this, searching for scientific papers on this topic at electronic resources of Cochrane library, PubMed, Embase and CENTRAL databases, resulted in only single reports on this issue [see References].

The purpose of the study was to assess micronephrolithiasis course features in children in the setting of oxidative stress.

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Materials and methods. There were examined 176 children from 1 to 18 years old with micronephrolithiasis who were tested and treated in the Public Nonprofit Enterprise "Ivano-Frankivsk Regional Children`s Clinical Hospital of Ivano-Frankivsk Oblast Council" during the period 2016–2019. Principal diagnosis was made based on modern guidelines [14] for diagnosis and treatment (e.g., Protocol of treatment of children with urinary tract infection and tubulointerstitial nephritis" No. 365 as of 20/07/2005), Medical management of kidney stones, guideline, approved by American Urology Association (2014) and criteria by D.D. Ivanova and O.M. Korzh.

According to the latter, to confirm the diagnosis of micronephrolithiasis (dysmetabolic nephropathy, kidney calculi), it is enough to assess crystal excess of different origin in the urine, verify positive echo-inclusions in the collecting system revealed at the kidney ultrasonography and also, establish the presence of isolated urinary syndrome in the sick child.

In accordance with the type of dysmetabolic nephropathy, distribution of patients in groups was conducted as follows: 1 – children with oxaluria (n=60, 34.1 %), 2 –patients with oxalate-calcium nephropathy, (n=53, 30.1 %); 3 – children with phosphate nephropathy, (n=33, 19.0 %), 4 – patients with uraturia (n=30, 17.0 %).

In case of oxalate nephropathy, urine pH is neutral (pH 5.0–7.0), there is an increase of oxalate level in 24-hour urinalysis above 1 mg/kg/day, calcium level above 4 mg/kg/day and above 2.68 mmol/L in the serum of blood. The greater number of urates in the urine was diagnosed in case of decrease of pH by more than 5.0, blood urea above 0.3 mmol/L and above 4.0 mmol/L/day in the urine. Phosphate nephropathy was confirmed in cases of pH elevation above 7.0 in the 24-hour urinalysis, phosphate level increase in the blood serum by more than 1.78 mmol/L and above 33 mmol/L/day in the urine.

Evaluation of general nitrite in the blood serum was conducted using a kit for measurement of general nitric oxide No. 110 DE1500, manufacturer RDS (UK), England. Reference value of general blood nitrite is 42.9±3.9 μmol/L.

Level of diene conjugates (DC) in blood plasma was evaluated using a method offered by V.B. Havrylov, A.R. Havrylova and Y.F. Khmara (2020). Assessment of TBA-active products of lipid peroxidation was made after E.N. Korobeinikova method (1989) using test with thiobarbituric acid. Its normal level in the blood serum is 3.55–3.85 μmol/L.

State of antioxidant system was assessed based on its enzyme chain – ceruloplasmin and catalase. Ceruloplasmin activity in the blood plasma was evaluated using N. Ravin method modified by H.O. Babenko (1999). Therewith, the norm is equal to 21 – 31 AU.

Catalase level evaluation in the whole blood was conducted using A.N. Bakh and S.A. Zubkova method (1997). Reference values of catalase in the blood of a healthy person are 9.52–12.52 mg/mL. Statistical result processing was conducted using a program package Statistics for Windows version 6.0 (Stat Soft inc., USA).

During the period of the research study there was an informed consent of a mother obtained for her child to participate in the study, the main principles of Declaration of Helsinki were followed (1975, with its further amendments in 2000). During the period of the research no biological experiments with involvement of vertebrates were conducted.

Results of the study and their discussion. As a result of our observation, greater number of children with pediatric microlithiasis were treated as out-patients and more seldom as in-patients (65.0 % i 35.0 %, $p<0.05$).

Among the criteria for admission can be distinguished the following: acute renal colic, haematuria and/or resistant proteinuria, acetonemic or intoxication syndrome, non-diabetic ketoacidosis, principal disease in the setting of which micronephrolithiasis occurred (diabetes mellitus, arterial hypertension, obesity of different origin, etc.).

Criteria of non-inclusion (withdrawal criteria) comprised: 1) malformations, autoimmune, hereditary and congenital kidney disease that were confirmed by all diagnostic methods; 2) acute and chronic renal insufficiency regardless of the stage; 3) chronic kidney disease; 4) concomitant and/or underlying decompensated disease; 5) parental and/or child`s refusal to participate in the study including not signing an informed consent; 6) mental and neurological disorders in patients with kidney disease; 7) acute and chronic infectious diseases.

By the moment of admission, mean duration of disease was 3.64±1.3 years in all age groups with renal microlithiasis without any exception. More often, there were representatives of younger and older pubertal age (30.27 and 37.39 %, $p>0.05$). Mean age of the examined children with renal microlithiasis was 11.2±5.4 years.

Distribution of the underlying disease, with several co-existing conditions simultaneously, in patients with renal microlithiasis looked like the following (fig. 1):

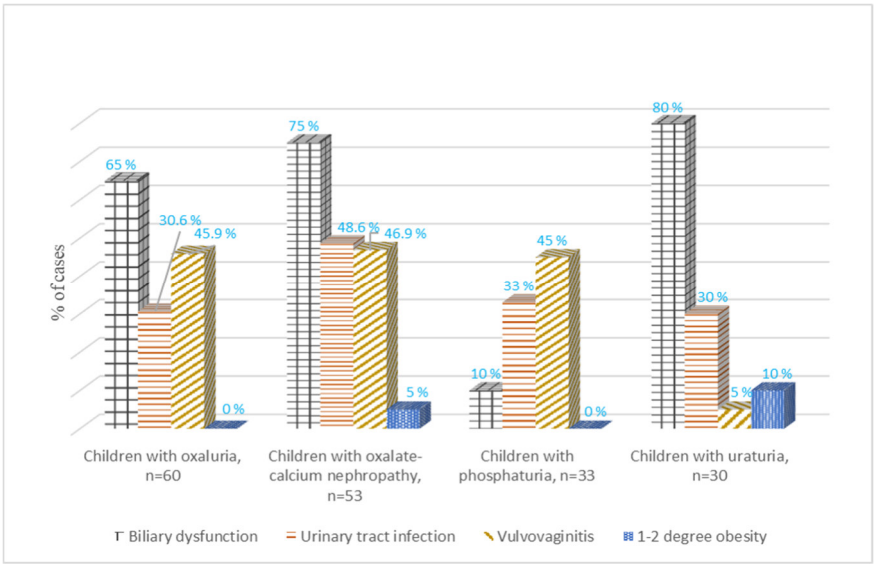

Fig. 1. The most common underlying disease in children with renal microlithiasis, n=176.

As we can see from the given data in fig. 1, the most common underlying disease in children with oxaluria and oxalate-calcium nephropathy is biliary dysfunction and urinary tract infections. In children with phosphaturia, among the concomitant disease, alimentary obesity is diagnosed more often.

It is worth pointing out that a number of aspects of renal microlithiasis clinical course features were determined by the course of the primary disease (fig. 2).

The obtained results demonstrate the prevalence of pain and intoxication syndromes in patients with different types of dysmetabolic nephropathy. Generally, in patients with micronephrolithiasis impaired posture (50.0 %), mitral valve prolapse (45.0 %), kyphosis (25.0 %) and multiple dysembryogenic stigmas (25.0 %) were observed.

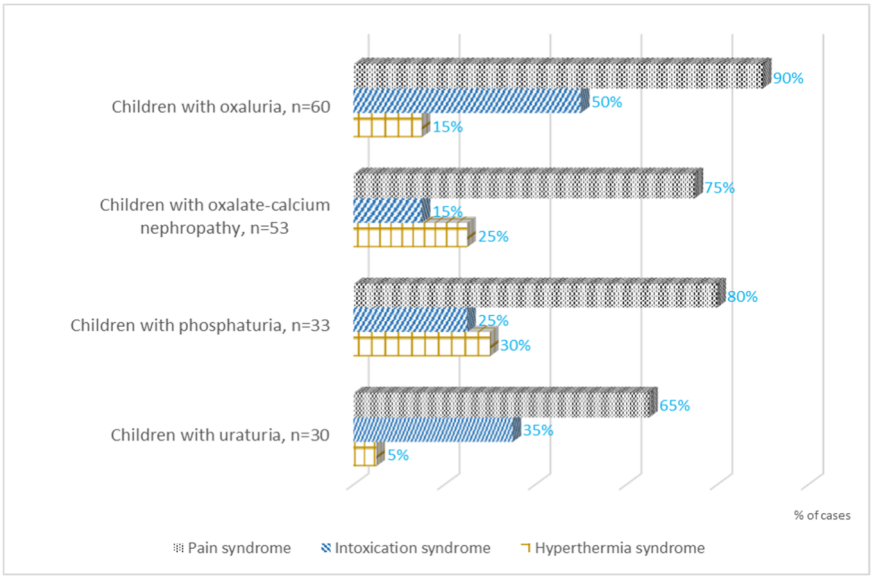

Fig. 2. Micronephrolithiasis clinical course features in children of different age associated with oxidative stress, n=176.

Taking into account that free radical oxidation impairment is considered to be an early and quite universal non-specific indicator of cell impairment and is typical for many pathological processes, we studied lipid peroxidation process state in the examined children with micronephrolithiasis depending on age and crystalluria type.

The data analysis obtained from 95 primary school-aged children with renal microlithiasis indicates elevation of DC level.

Herewith, the most significantly, these parameters were increasing with uraturia and to lesser extent with oxaluria. Thus, the median level of diene conjugates in 20 patients with uraturia was 3.06±0.7 AU/mL compared to norm 1.45±0.7 AU/mL ($p<0.05$), in children with oxaluria (n=26) the median level of diene conjugates was 2.65±0.6 AU/mL ($p<0.05$). In 26 patients with oxalate-calcium nephropathy level of diene conjugates was 3.01±0.7 AU/mL ($p<0.05$).

The least change of these parameters compared to norm was observed in phosphaturia (2.00±0.6 AU/mL, ($p<0.05$).

In subjects from the control group the parameter level was within the reference values (1.45±0.7 AU/mL).

With regard to TBA-active products of lipid peroxidation we found its statistically significant decrease in patients with all types of renal microlithiasis. Patients with phosphaturia showed the level of TBA active products of 3.32±0.13 μmol/L (reference value 3.69±0.14 μmol/L, $p<0.05$). In patients with uraturia more significant decrease was observed: TBA active products were at the level of 3.20±0.12

μmol/L (p<0.05). In patients with oxaluria its level was 2.68±0.13 μmol/L (p<0.05). The lowest level was in patients with oxalate-calcium nephropathy of 2.13±0.11 (p<0.05).

In the group of adolescent patients there were more significant changes from the side of lipid peroxidation processes and proteins, accumulation of TBA-active products that results in endogenous intoxication development (table 1).

Table 1

Parameters of lipid peroxidation in children of senior school age with micronephrolithiasis, n=81

Patients, absolute number, %	Parameter of lipid peroxidation			
	$D_{232}/_{0,1\ mL\ of\ plasma}$, AU/mL	Norm, AU/mL	TBA-active products, μmol/L	Norm, μmol/L
Patients with oxaluria, n=34 (42%)	6.05±0.6*	1.45±0.7 p<0.05	2.02±0.13*	3.69±0.14 p<0.05
Patients with oxalate-calcium nephropathy, n=27 (33%)	5.01±0.6**	1.45±0.7 p<0.05	4.01±0.13**	3.69±0.14 p<0.05
Patients with phosphaturia, n=10 (12.5%)	2.60±0.11***	1.45±0.7 p<0.05	3.02±0.12***	3.69±0.14 p<0.05
Patients with uraturia, n=10 (12.5%)	4.25±0.7****	1.45±0.7 p<0.05	2.35±0.7****	3.69±0.14 p<0.05

Note. *Statistical significance of differences between the parameters of diene conjugates and malonyldialdehyde in children with oxaluria and control data, ** Statistical significance of differences between the parameters of diene conjugates and malonyldialdehyde in children with oxalate-calcium nephropathy and control data, *** Statistical significance of differences between the parameters of diene conjugates and malonyldialdehyde in children with phosphaturia and control data, **** Statistical significance of differences between the parameters of diene conjugates and malonyldialdehyde in children with uraturia and control data

As indicated by the obtained data, parameters of lipid peroxidation were changing significantly with oxaluria, while with other types of pediatric renal microlithiasis common was only limited activation of these processes. Through the course of the research blood catalase level was assessed in children suffering from kidney calculi in comparison with its blood concentration in virtually healthy children (table 2).

Table 2

Parameters of an antioxidant system in patients with renal microlithiasis

Mean parameter value	Age	Healthy subjects (n=30)	Children with renal microlithiasis (n=176)			
			Patients with oxaluria, n=60	Patients with oxalate-calcium nephropathy, n=53	Patients with phosphaturia, n=33	Patients with uraturia, n=30
Cerulo plasmin, relative units	6 to 12 years	21.00±0.02*	29.54±0.01 p<0.05**	30.11±0.02 p<0.05****	23.20±0.02 p>0.05****	30.65± 0.01 p<0.05*****
	10 to 12 years	26.65±0.01*	30.45±0.02 p<0.05**	31.05±0.01 p<0.01***	27.70±0.01 p>0.05****	32.50±0.01 p<0.05*****
	13 to 17 years	29.45±0.01*	40.39 ±0.02 p<0.05**	26.11±0.01 p<0.01****	28.45±0.01 p>0.05****	38.41±0.02 p<0.05
Catalase, mg/mL	10 to 12 years	11.71±0.02*	13.61±0.01 p<0.05**	12.85±0.01 *** p<0.01	12.00±0.03 **** p>0.05	12.91±0.01 ***** p<0.05
	13 to 17 years	11.12±0.01	14.76±0.02 p<0.05**	11.22±0.02 p<0.01	13.20±0.03 p<0.05	13.03±0.02 p<0.05

Note: *Data from the conducted research, **Statistical significance of differences between the parameters of ceruloplasmin, catalase in healthy children and patients with oxaluria, *** Statistical significance of differences between the parameters of ceruloplasmin, catalase in healthy children and patients with uraturia, **** Statistical significance of differences between the parameters of ceruloplasmin, catalase in healthy children and patients with phosphate-calcium nephropathy, ***** Statistical significance of differences between the parameters of ceruloplasmin, catalase in 10–12-year-old children with oxaluria and healthy children

In accordance with the obtained data, median ceruloplasmin activity in children with oxaluria and uraturia was higher in adolescence, in particular in the age group of 13–17-year-old children. Also, median catalase activity was changing towards an increase in particular in this age group.

Median nitrite level was the most significantly decreased in senior-school age children (13–17 years old) with oxaluria compared to healthy adolescents (30, 53 and 41.3 μmol/L, p<0.05) and its maximum levels were registered in patients of this age group with phosphaturia (37.11 and 41.30 μmol/L, p<0.01). In subjects of other age groups who were diagnosed with uraturia and oxalate-calcium nephropathy respectively, total nitrite level did not differ from norm.

Despite the ambiguity of terminology, variable interpretation of approaches to the diagnosis and treatment of the disease, interest in the study of micronephrolithiasis in childhood is steadily growing, as evidenced by research in the recent years [1, 10, 11, 15].

Apart from this, there are ongoing studies of the oxidative stress role in the pathogenesis of metabolic kidneys disease in childhood [1, 2, 8]. Their authors also discuss the use of antioxidants in the complex therapy of metabolic and infectious kidney conditions in children and adults [3, 6, 7].

At the same time, we have found a lack of domestic scientific literature due to this issue, and the review of foreign data over the past decades is sometimes controversial thus requiring further study [1, 2, 9, 13, 15].

Today, the most scientists agree on more significant oxidative stress in children with oxaluria and oxalate-calcium nephropathy [1, 4, 9, 11]. It also has been described in our scientific work.

The prevalence of the mentioned types of metabolic nephropathy in children is age- and gender-depended; it can be explained by the presence of increasing rate of comorbidities such as obesity, diabetes mellitus, and hypertension, etc. [5, 7].

Although, certain scientists have found no significant differences in gender and age between children with metabolic nephropathy, and insist on a genetic component in the pathogenesis of the condition [4].

In many ways, our results are similar to observations of some researchers [1], who established a certain dependence of the oxalate excretion levels on gender (it occurs mainly in females), as well as a likely increase in aldehyde and ketone-derivatives of the main character ($p<0.05$) with moderate and high excretion of oxalates.

More than that, we found an increased activity of the primary products of lipoperoxidation (diene conjugates) in the blood of children with uraturia. The average nitrite level was significantly lower in patients with phosphaturia. In teenagers, the last indicator did not change with age. The conclusions we've made in scientific research also coincide with the opinion of other researchers: micronephrolithiasis in childhood is accompanied by significant activity of lipoperoxidation processes.

Conclusion

Therefore, an increase of primary products of lipid peroxidation (DC) in blood is evident of free radical process activation in children with micronephrolithiasis. Simultaneously, a reduction of TBA-active substances together with an elevation of indices of the antioxidant system of the body are the evidence of activation of adaptation mechanisms to compensate pathological changes induced by free oxygen radical molecules in children with metabolic kidney disease.

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