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MICROALBUMINURIA AS A DIAGNOSTIC MARKER OF TUBULOINTERSTITIAL KIDNEY DAMAGE IN CHILDREN WITH SECONDARY OXALATE NEPHROPATHY

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SUMMARY

In recent decades, the problem of nephrolithiasis has become more and more urgent among children and adults. It has been established that nephrolithiasis in almost 75 - 80% of cases consists of calcium salts, namely calcium oxalate (CaOx), which enters the body through food, but the bulk is formed endogenously. It has been determined that hyperoxaluria is common in diabetic and obese patients, contributing to an increased risk of stone formation. Moreover, untimely detected hyperoxaluria in childhood can lead to transformation into nephrolithiasis in adults. The main reason for close attention to hyperoxaluria is associated with complications in the form of nephrolithiasis, persistent urinary tract infection, interstitial nephritis and other manifestations, even in the first years of a child's life. In this regard, it is necessary to search for early diagnostic markers, including damage to the tubulointerstitial canal in children with hyperoxaluria. In recent years, there has been a marked increase in interest in microalbuminuria (MAU) as a marker of kidney damage. Considering the above, in our study we studied the age and gender characteristics, the effect of metabolic disorders on the development of secondary oxalate nephropathy (SON), the characteristics of urinary syndrome for this pathology, as well as the determination of MAU in children with SON. The results we obtained showed that in most cases we established the enteral type of SON. At the same time, a reliably significant relationship was determined between the degree of oxaluria and microalbuminuria in urine in children with enteral and idiopathic types of SON. Microalbuminuria was more pronounced in children with kidney microliths.

KEYWORDS: microalbuminuria, diagnostic marker, children, secondary oxalate nephropathy.

INTRODUCTION

The problem of dysmetabolic nephropathy (DN) is quite relevant in pediatrics and pediatric nephrology. This is due to the high frequency of DN in the population, as well as the possibility of their progression up to the development of urolithiasis and / or tubulo-interstitial nephritis.

Tubulo-interstitial kidney disease (TIKD) associated with congenital or hereditary and metabolic nephropathies, uropathies with impaired urodynamics complicated by renal infection, reflux nephropathy (RN) in the structure of CKD causes occur from 22% (North American Pediatric Renal Transplant Cooperative Study, 2010) to 57.6% (European Renal Association-European Dialysis Transplant Association, 2012).

Predictors of the initiation of interstitial damage and the progression of tubulo-interstitial kidney damage in children are immunological (an increase in the production of pro-inflammatory, prosclerotic cytokines and growth factors with a decrease in the production of anti-inflammatory cytokines); hemodynamic (decrease in Vs, Vd), clinical and paraclinical (arterial hypertension, microalbuminuria, renal infection, glomerular filtration rate) factors. The leading predictors of the formation of tubulo-interstitial kidney damage in children with vesicoureteral reflux and its progression in patients with reflux nephropathy are immunological, whose contribution during formation is 38.05%, with a progression of 42.1%.[24-25]

Therefore, in recent years, there has been a marked increase in interest in microalbuminuria (MAU) as a predictor of nephropathy.[1] Albuminuria is a well-known predictor of adverse renal outcomes in patients with type 2 diabetes mellitus and hypertension,[2] so patients with microalbuminuria usually progress to proteinuria and overt diabetic nephropathy. This is accompanied by an increased level of CRP, which indicates the activation of inflammatory pathways during the progression of atherosclerotic kidney and cardiovascular disease.[3]

In addition, microalbuminuria as a preclinical marker of kidney damage often acts as a predictor of sickle cell nephropathy (SCN) and is one of the earliest signs of this pathology. At the same time, in the adult population, microalbuminuria was recorded in 68% of cases,[4] and in children, the prevalence of microalbuminuria ranged from 15.5 to 47.1%.[5]

Microalbuminuria occurs when urinary albumin levels are significantly higher than normal and is diagnosed when urinary albumin excretion is 30 to 300 mg / day or when the microalbumin / creatinine ratio is 30 to 300 μg / mg in spontaneous urine.[6] It has been shown to be an early predictor of renal and cardiovascular disease not only in patients with diabetes mellitus or hypertension, but also in the general population.[7]

Several studies in obese children and adolescents have identified specific risk factors associated with the detection of microalbuminuria. They include body mass index (BMI), waist circumference (WC), triglycerides (TG), gender, and metabolic syndrome in children and adolescents.[8-11]

Chronic kidney disease (CKD) has become a public health problem worldwide, and microalbuminuria is an early marker of CKD.[21] Many studies have shown that microalbuminuria is a prognostically important and independent predictor of the progression of kidney disease, cardiovascular complications, and all-cause mortality in non-diabetic, hypertensive patients, and even in the general population.[12-16]

C-reactive protein (CRP) is recognized as a sensitive marker of inflammation. Several concurrent studies have found a significant correlation between CRP and microalbuminuria in the general population.[17,18] however, other studies have shown conflicting results.[19,20]

Damage to the tubular apparatus occurs at the early stages of the development of nephropathy, even before the appearance of obvious clinical signs, and dysfunction of the endothelium develops long before the onset of structural changes in the kidneys. Moreover, the change in the parameters of endothelium-dependent vasodilation occurs in parallel with a decrease in the glomerular filtration rate and correlates with the levels of biomolecular markers of inflammation.[22]

Morphologically, the destruction of the apical surfaces of the epithelium of the renal tubules, lymphohistiocytic infiltration of the interstitium is revealed. Crystals of calcium oxalate are found in the lumen of the tubules and interstitium. With the progression of the disease, sclerosis phenomena, the involvement of glomeruli are noted. In the case of a progressive course of the disease, taking into account the peculiarities of the pathogenesis, it is possible to develop tubulointerstitial nephritis, urolithiasis, and recurrent pyelonephritis.[23]

In connection with the above literature data, in our study, we wanted to study the prognostic value of MAU in children with secondary oxalate nephropathy (SON).

THE PATIENTS

A prospective analysis of the results of a survey of 106 children aged 6 months to 7 years was carried out. The main group consisted of 76 children diagnosed with secondary oxalate nephropathy. Taking into account anamnestic data and clinical characteristics, children in the main group were divided into 3 subgroups. 45 children with enteral type of secondary oxalate nephropathy, 20 children with dietary type and 11 children with idiopathic type. The control group consisted of 30 children with calcium oxalate crystalluria without clinical signs of secondary oxalate nephropathy (SON). Patients with primary hyperoxaluria, hyperparathyroidism, urinary tract infection, thyrotoxicosis, obstructive nephropathy, autoimmune diseases, and diabetes mellitus were excluded from the study.

MATERIAL AND METHODS

The following data were taken from the child's outpatient card: age, sex, life history, medical history of the child, frequency of prescribed and taken antibiotic therapy over the last 6 months. Parents of children were interviewed for the presence of chronic diseases, the nature and characteristics of the diet of children under 12 months and after, the nature of the volume of fluid consumed during the day. We determined the anthropometric parameters (height, weight of the child), and also measured blood pressure (systolic and diastolic), and calculated the body mass index. The diagnosis of oxalate nephropathy was verified on the basis of generally accepted clinical and laboratory (complete blood count, urine, urine flow cytometry, urine analysis according to Nechiporenko, determination of oxalates in daily urine, biochemical blood test: determination of total protein, albumin, creatinine, calcium, potassium, phosphorus, magnesium in the blood) and instrumental research methods (ultrasound). All children in the study groups were analyzed for intestinal microflora. The determination of the daily excretion of oxalates was carried out by the titrimetric method of permanganatometry. Hyperoxaluria was an increase in oxalates above 0.5 mg / kg / day. The MAU content was determined using a standard kit for all children, before and after the treatment. A reading of 30 mg / dL and above was perceived as microalbuminuria. The ultrasound examination was carried out using a Siemens Acusson S3000 apparatus. To determine GFR, the Schwarz formula was used: Ccr = K * L / Cr, where Ccr is glomerular filtration in ml / min * 1.73 m2; Serum Cr-creatinine (mg / dL); L-child's height in cm; K - coefficient equal to 0.45 for children under one year old, 0.55 for children aged 1-18. The conversion of serum creatinine from mmol / L to mg / dL (mg%) was carried out by multiplying this value by 11.3.

RESULTS

Table 1: Distribution of patients by study groups.

	Main group			Control group (n = 30)
	Enteral type (n = 45)	Dietary type (n = 20)	Idiopathic type (n = 11)	
Age (years) (av ± sd)	3.35 ± 1.94	5.05 ± 1.82	3.45 ± 1.81	3.83 ± 2.05
Floor				
Boys	15 (33.3%)	10 (50.0%)	8 (72.7%)	18 (60.0%)
Girls	30 (66.7%)	10 (50.0%)	3 (27.3%)	12 (40.0%)

av - average
sd – standard deviation

The study of the age structure in Table 1, reflected the heterogeneity of the groups of children by age, in whom the development of SON took place. It can be seen from the table that SON with enteral and idiopathic types were found in young children (cf ± c 3.35 ± 1.94 and cf ± c 3.45 ± 1.81, respectively), and in the group of children with food type, SON developed at an older age (cf ± c 5.05 ± 1.82). In the control group with calcium oxalate crystalluria, the average age was 3.83 ± 2.05.

The table shows that most often SON with enteral type developed in girls (66.7%, n = 30), in contrast to the idiopathic type, where it was more common in boys (72.7%, n = 8). In children with the dietary type, SON was equally found in both girls and boys. We also carried out an analysis of anthropometric indicators in children in the study groups, which showed that children in the main study group with food type SON in 25% of cases had excess body weight and in 10% of cases obesity. Overweight and obesity were caused by the abuse of soda, fatty foods, cocoa milk products, chocolate and fast foods as noted in chapter 3. 60% of children had a normosthenic body type. In the study group in children with the enteral type of SON, 17.8% of children were overweight, 11.1% of children were obese, and 22.2% of children were underweight. In this group, most of the children were underweight, which was associated with malabsorption syndrome, with frequent ARI. In the group of children with an idiopathic type of SON course, the majority of children (72.8%) had a normosthenic body type. 18.2% of children were underweight. In the control group of the study, 96.6% of children had a normosthenic body type.

Table 2: Anthropometric indicators of children in the study groups.

	Main group			Control group (n = 30)	p-value
	Enteral type (n = 45)	Dietary type (n = 20)	Idiopathic type (n = 11)		
Height (Me [IQR])	92 [80 - 115]	116.5 [107-122.5]	102 [89 - 114]	111 [82 - 115]	0.020
Weight Me [IQR])	15.0 [11.8-18.2]	22.5 [18.0-26.0]	14.0 [13.0 - 20.5]	17.5 [11.0 - 21.5]	0.006
BMI	17.3 ± 3.80	18.0 ± 3.95	16.7 ± 3.50	16.5 ± 1.66	0.488
Body mass index percentile	62.6 (36.5)	67.5 (34.1)	47.4 (36.9)	55.5 (31.2)	0.371
BMI Results					
Norm	22 (48.9%)	12(60.0%)	8 (72.7%)	29 (96.6%)	
Overweight	8 (17.8%)	5 (25.0%)	0 (0%)	1 (3.3%)	
Obesity	5 (11.1%)	2 (10%)	1 (9.1%)	0 (0%)	
Underweight	10 (22.2%)	1 (5.0%)	2 (18.2%)	0 (0%)	0.033

Urinalysis in 76 children with secondary oxalate nephropathy revealed significant changes in urinary sediment. It should be noted that the changes in urinary sediment in the compared groups were different. In children in the group with the enteral type of SON, calcium oxalate crystalluria was detected in 35.6% of children in grade 3+, in 28.9% of children in a total number, in 22.2% in 2+ and 13.3% in 4+. Deviations in urine analysis in this group of children were more pronounced and represented by calcii oxalate cristaluria (COC), proteinuria (71.1%), microhematuria on average 7 in the field of view. In children with dietary type SON in 55% of cases oxalates were noted in the amount of 3+, in 15% 1+ and 2+, 1 child had 4+, and in 2 (10%) children in the amount of splash in the field of view. Proteinuria in trace form was detected in 20% of children, and erythrocytes averaged 6.5 in the field of vision.

In the group with the idiopathic type of SON, COC was also most common (45.5%) in the amount of 3+. In this group, microhematuria was more pronounced, which averaged 5 erythrocytes per field of view.

In the control group, COC was also detected in the amount of 3+ and 2+ (46.7% and 50%, respectively). Other indicators were within normal limits.

Table 3:Comparative characteristics of morning urine sediment in children in the study groups.

Parameters	Main group			Control group (n = 30)	p-value
	Enteral type (n = 45)	Dietary type (n = 20)	Idiopathic type (n = 11)		
Oxalates in morning urine					
1+	0 (0%)	3 (15.0%)	0 (0%)	1 (3.3%)	
2+	10 (22.2%)	3 (15.0%)	4 (36.4%)	15 (50.0%)	
3+	16 (35.6%)	11 (55.0%)	5 (45.5%)	14 (46.7%)	
4+	6 (13.3%)	1 (5.0%)	0 (0%)	0 (0%)	
All over	13 (28.9%)	2 (10.0%)	2 (18.2%)	0 (0%)	<0.001
Proteinuria	32 (71.1%)	4 (20.0%)	2 (18.2%)	0 (0%)	<0.001
Red blood cells in urine (Me [IQR])	7.0 [4.0-12.0]	6.5 [3.5-10.5]	5.0 [4.0-14.5]	0.0 [0.0-0.0]	<0.001

Biochemical analysis of urine to determine the excretion of oxalates during the day in children in the study groups showed that in the group of children with enteral type of SON, the average level of excretion of oxalates during the day with urine averaged 0.86 ± 0.25 mg / kg / day, with the norm is 0-0.5 mg / kg / day. In children in the group with the dietary type and with the idiopathic type of SON, this indicator had significantly low values compared with the enteral group, 0.68 ± 0.08 and 0.70 ± 0.16 mg / kg / day, respectively, but was higher compared to the control group. In the control group, the average level of excretion of oxalates during the day with urine was 0.26 ± 0.09 mg / kg / day, which is the norm. In children in the control group (children with PCC) oxalates were detected in one-time urine tests, with normal excretion of oxalates in daily urine.

Urinary syndrome, along with increased urinary excretion of oxalate salts, was represented by microalbuminuria. Microalbuminuria was more common in children with enteral and idiopathic SON types and averaged 30 mg / dL. In the control group, urine microalbumin was on average within the normal range and amounted to 10 mg / dL. (p <0.001).

Table 4:Comparison of urine microalbumin levels with daily urine oxalate levels.

	Main group			Control group (n = 30)	p-value
	Enteral type (n = 45)	Dietary type (n = 20)	Idiopathic type (n = 11)		
Microalbumin in urine (mg/dL) (Me [IQR])	30.0 [20.0-50.0]	20.0 [10.0-30.0]	30.0 [20.0- 35.0]	10.0 [10.0-18.75]	<0.001
Daily oxalates (0-0.5 mg / kg / day)	0.86 ± 0.25	0.68 ± 0.08	0.70 ± 0.16	0.26 ± 0.09	<0.001

DISSCUSION

Thus, a reliably significant relationship was established between the degree of oxaluria and microalbuminuria in urine (p <0.001) in children with enteral and idiopathic types of SON. Microalbuminuria was more pronounced in children who had microliths in the kidneys.

CONCLUSIONS

SON developed most often in children with gastrointestinal disorders that occurred in young children with a greater frequency in girls than in boys. Children in the main group with enteral and idiopathic types of SON in comparison with other groups had consistently high MAU values.

The high frequency of detection of MAU in children with secondary oxalate nephropathy allows it to be recommended for the diagnosis of tubulo-interstitial kidney damage in the early stages, as well as for monitoring the progression of renal parenchyma lesions.
The relationship between the development of tubulo-interstitial kidney damage in children with SON and an increase in MAU levels in dynamics was revealed, which proved the possibility of using this indicator as an early marker of endothelial dysfunction and prognostically unfavorable course of oxalate nephropathy in children.

Long-term and frequent use of antibiotic therapy leads to enteric hyperoxaluria. In the presence of a history of the ICD in children with enteric hyperoxaluria, the degree of risk of developing oxalate nephropathy increases.

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