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Urinary metabolic abnormalities in children with idiopathic hematuria

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Summary

Background
Hematuria, either macroscopic or microscopic, is an incidental finding of multiple nephrologic or urologic disorders. Disturbances of urine inhibitors or promotors have been suggested as the potential causes of isolated idiopathic hematuria in children and its recurrence. Meanwhile, appropriate treatment of these risk factors might improve secondary asymptomatic or macroscopic hematuria.

Objectives
The aim of this study was to identify contribution of urinary biochemical abnormalities in children with isolated idiopathic hematuria.

Methods
About 522 children with isolated hematuria were evaluated in a prospective cross-sectional study. Data such as clinical manifestations, family history, laboratory examinations, structural anomalies, and urine biochemistry were obtained. Patients with nephrolithiasis, nephrocalcinosis, tubulointerstitial disorder, genitourinary abnormality, urinary tract infection, and glomerular disorder were excluded from the study. Variables such as calcium, citrate, oxalate, phosphate, uric acid, cystine, and magnesium were measured in 24-h urine collection. In addition, serum levels of electrolytes, urea, creatinine, parathyroid hormone, and bicarbonate were identified.

Results
Mean age at diagnosis was 5.9 years, and females outnumbered males (2/1). Of those, 88.5% had microscopic hematuria, and 12.6% experienced episodes of gross hematuria. Abdominal pain was the most common clinical manifestations. Urinary tract infection occurred in 30% of cases. Totally, 94% of patients had single or multiple metabolic abnormalities in 24-h urine excretion including hypocitraturia, 60.7%; hypomagnesuria, 58.2%; hyperuricosuria, 35.8%; hypercalciuria, 33.7%; hyperoxaluria, 33.7%; and cystinuria, 0.76%, respectively. About 8% of cases had mixed urine metabolic disturbances. Most patients had mild hematuria (red blood cell <10/high power field (hpf)), and 18% had significant hematuria (>30/hpf), with no statistical correlation to urine metabolic abnormalities. About 80% of patients had a history of nephrolithiasis in their relatives.

Discussion
Decreased urinary inhibitor concentration followed by increased stimulator concentration were the most common abnormalities in patients with idiopathic hematuria. Accordingly, measurement of urinary biochemical concentration is highly recommended in children with isolated hematuria. In addition, investigating the therapeutic effect of potassium citrate supplements is highly recommended in these patients to prevent future stone formation and treatment of hematuria.

Variables	No (%)	<5 years old (%)	Female (%)	FH of NL (%)	Gross hematuria (%)
Hypocitraturia	60.7	70.9 ($p < 0.001$)	66.6 ($p = 0.9$)	80.1 ($p = 0.9$)	11 ($p = 0.9$)
Hypomagnesuria	58.2	64.9 ($p = 0.008$)	71.1 ($p = 0.005$)	81.3 ($p = 0.5$)	10.5 ($p = 0.98$)
Hyperuricosuria	35.8	39.6 ($p = 0.12$)	61.2 ($p = 0.77$)	84 ($p = 0.11$)	10.2 ($p = 0.47$)
Hypercalciuria	33.7	28.5 ($p = 0.2$)	65.8 ($p = 0.9$)	83.6 ($p = 0.26$)	10.4 ($p = 0.66$)
Hyperoxaluria	24.9	27.1 ($p = 0.3$)	70.8 ($p = 0.2$)	78.5 ($p = 0.5$)	11.5 ($p = 0.68$)

FH, familial history; NL, nephrolithiasis.

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Introduction

Idiopathic hematuria is an important diagnostic and challenging dilemma in children. Asymptomatic hematuria is an important manifestation of nephrologic or urologic disorders with an incidence of 0.4–4.1%. Isolated idiopathic hematuria is considered after exclusion of all pathophysiologic mechanisms of hematuria, which needs multiple diagnostic procedures for an accurate diagnosis [1].

Urinary biochemical abnormalities are considered the potential reversible causes of asymptomatic idiopathic hematuria in both children and adults [1,2].

An imbalance between urinary promotors (calcium, urate, cystine, and oxalate) and inhibitors (phosphate, magnesium, citrate, nephrocalcin, and glycosaminoglycan) excretion has been suggested in the pathogenesis of idiopathic hematuria rather than any single abnormality [3,4].

In fact, hematuria of unknown origin might frequently occur in patients with hypercalciuria and hyperoxaluria and less commonly in patients with hyperuricosuria, which could improve with specific treatment of the related abnormality [1].

The purpose of this study was to identify urinary biochemical excretion rate in children with unexplained isolated microscopic or macroscopic hematuria.

Materials and methods

This prospective cross-sectional cohort study was performed in children younger than 5 years with idiopathic hematuria, who are referred to the nephrology clinics between July 2011 and March 2017. It was approved by the local ethics committee and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from legal guardians of the involved patients.

Patients with definite causes of hematuria such as nephrolithiasis, urinary tract infection, genitourinary abnormalities, glomerular or tubular disorders, renal insufficiency, abnormal blood gas analysis, severe obesity, immobilization, and drug-induced abnormalities (corticosteroids, diuretics, and anticonvulsants) were excluded. Clinical manifestations, laboratory findings, and radiologic examinations were evaluated in all cases.

Twenty-four–hour urine collection was performed on a usual diet for one or two times and analyzed for metabolic risk factors including calcium, citrate, oxalate, phosphate, uric acid, cystine, and magnesium levels. In addition, the urine was collected in 2 separate containers with HCl for the measurement of urine calcium content and without additional substance. In addition, serum levels of sodium, potassium, calcium, phosphorus, urea, creatinine, alkaline phosphatase, parathyroid hormone, and blood gas values were measured.

Serum and urine calcium were measured by ion-selective electrode method. Serum and urine magnesium and phosphate were identified using an automated analyzer. Uric acid was calculated by the uricase method. In addition, serum and urine creatinine were measured by Jaffe kinetic method.

Urine citrate and oxalate were determined by the enzymatic procedure. Urinary cystine excretion was documented by detection of hexagonal urinary cystine crystals and discoloration of sodium nitroprusside.

Abnormal values for urine biochemicals were based on published criteria in children with urolithiasis [5] including hypercalciuria, urine calcium >4 mg/kg/day; hyperoxaluria, urine oxalate >0.5 mmol/1.73 m^2 body surface area (BSA)/day; hyperuricosuria, urine uric acid >815 mg/1.73 m^2 BSA/day; hypocitraturia, urine citrate <320 mg/1.73 m^2 BSA/day; and hypomagnesuria, urine magnesium <88 mg/1.73 m^2 BSA.

Continuous variables were expressed as mean $\pm$ standard deviation, and discrete variables were identified as percentage. The χ^2 and Fisher's exact tests were used to identify significant difference between proportional nominal data. Meanwhile, numerical data were compared by the student's t-test. A p value < 0.05 was considered statistically significant.

Results

A total of 681 patients with hematuria were evaluated in this study. Of them, 159 cases were excluded for associated nephrolithiasis or glomerular disorders.

About 88.5% of 522 enrolled patients had isolated microscopic hematuria, and 11.5% presented with gross hematuria at the beginning of presentation. Mean age at the time of diagnosis was 5.9 years (range: 1–14.5), and 66% were females.

Occasional abdominal pain was the most common symptom in 74.5% of patients. Most patients (80.3%) had a history of nephrolithiasis in their relatives (Table 1).

Urine metabolic abnormalities were identified in 94% of cases, with the predominance of hypocitraturia, followed by hypomagnesuria, hyperuricosuria, hypercalciuria, hyperoxaluria, and cystinuria (Table 2). Hypocitraturia, hypercalciuria, hyperuricosuria, and hyperoxaluria were identified in 68% ($p < 0.001$), 21% ($p = 0.002$), 31% ($p = 0.01$), and 22% ($p = 0.11$) of patients with hypomagnesuria, respectively. In addition, 20–68% of cases with hypomagnesuria had associated increased calcium, uric acid, and oxalate excretion, and hyperuricosuria was found in 51.4% of patients with hypercalciuria ($p < 0.001$).

RBC count was <10/hpf in 42%, 10–30/hpf in 40%, and >30/hpf in 18% of patients, which had no significant correlation with urine metabolic abnormalities.

Table 1 Characteristics of children with asymptomatic hematuria.

Variables	No (%)	<5 years old (%)	Female (%)
FH of stone	80.3	84.7 ($p = 0.02$)	79.7 ($p = 0.98$)
Abdominal pain	74.5	71.4 ($p = 0.17$)	78.8 ($p = 0.002$)
Dysuria	40.6	41.4 ($p = 0.73$)	49.5 ($p < 0.001$)
UTI	31	30.8 ($p = 0.94$)	39.1 ($p < 0.001$)
Gross hematuria	12.6	13.3 ($p = 0.25$)	9.5 ($p = 0.05$)

FH, familial history; UTI, urinary tract infection.

Table 2 Urinary biochemistry in children with asymptomatic hematuria.

Variables	No (%)	<5 years old (%)	Female (%)	FH of NL (%)	Gross hematuria (%)
Hypocitraturia	60.7	70.9 ($p < 0.001$)	66.6 ($p = 0.9$)	80.1 ($p = 0.9$)	11 ($p = 0.9$)
Hypomagnesuria	58.2	64.9 ($p = 0.008$)	71.1 ($p = 0.005$)	81.3 ($p = 0.5$)	10.5 ($p = 0.98$)
Hyperuricosuria	35.8	39.6 ($p = 0.12$)	61.2 ($p = 0.77$)	84 ($p = 0.11$)	10.2 ($p = 0.47$)
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Hyperoxaluria	24.9	27.1 ($p = 0.3$)	70.8 ($p = 0.2$)	78.5 ($p = 0.5$)	11.5 ($p = 0.68$)

FH, familial history; NL, nephrolithiasis.

Discussion

Urinary biochemical abnormalities are important causes of asymptomatic idiopathic hematuria in pediatric patients [1]. Microcrystallization with uroepithelial damage is the essential mechanism of persistent isolated microscopic hematuria or recurrent macroscopic hematuria in these patients in the absence of nephrolithiasis [6].

Most of the study patients had microscopic hematuria vs gross hematuria. In the study by Spivacow et al. [1] on 60 children with idiopathic hematuria and crystalluria, 88.3% had gross hematuria, followed by microhematuria in 11.7% and both types of hematuria in 5.1% of patients.

Screening of urine biochemical excretion has been suggested in patients with recurrent abdominal or flank pain, voiding dysfunction, urinary tract infection, osteopenia, frequency-dysuria syndrome, genital bleeding, enuresis, red urine, isolated persistent microscopic hematuria, recurrent gross hematuria, hereditary hematuria, and familial history of nephrolithiasis [7,8]. Abdominal pain was the most common symptom of crystalluria in the study patients. However, none of the patients suffered from abdominal or flank pain in the other reports.

About 80% of the study patients had a family history of nephrolithiasis in their first or second degree relatives, compared with 40–79% in the previous studies [1], which could be related to the higher incidence of consanguinity in the study parents.

Idiopathic *hypercalciuria* has been reported in children with hematuria since 1980s and early 1990s, when renal ultrasound was increasingly used [9]. It has been reported in 30–43.5% of patients with isolated microscopic hematuria and in 15.5–22.5% of those with gross hematuria [1]. Similarly, about 30% of the study patients had idiopathic hypercalciuria after exclusion of all pathologic causes of increased urine calcium excretion.

Lowering urine calcium excretion by protein and salt restriction, increased fluid intake, and thiazide and citrate compounds have been recommended in patients with persistent hypercalciuria, recurrent macroscopic hematuria, or recurrent nephrolithiasis. However, hematuria might recur after withdrawal of thiazide treatment [6,10,11].

Hyperuricosuria is defined as urinary uric acid excretion of more than 95% of normal values, which accounts for 5–20% of recurrent hematuria in children. About 30% of the study patients had increased urinary uric acid excretion with normal serum uric acid level. Restriction of purine intake and treatment with allopurinol decreased uric acid level with resolution of hematuria over 6–12 months in the study by Perrone et al. [12].

Primary *hyperoxaluria* is highly suspected in children with recurrent nephrolithiasis or unexplained hematuria through a mechanism similar to hypercalciuria and hyperuricosuria [13]. In fact, unexplained hematuria was the most common manifestation of patients with hyperoxaluria in the study by Alimardini et al. [14] and found in 11.7% of cases in the study by Spivacow [1]. Therapeutical approaches such as increased fluid intake and pyridoxine, citrate, and magnesium preparations have been recommended for treatment of hyperoxaluria and associated hematuria [15]. About one-third of the study patients had primary renal hyperoxaluria >0.5 mmol/1.73 m^2/d without nephrolithiasis, nephrocalcinosis, and severe hyperoxaluria.

Clinical manifestations of *cystinuria* occur secondary to stone formation and [5] and might improve with normalization of urine cystine excretion [16]. Considering low incidence of cystinuria, only 4 patients had cystine excretion in the study, and none of them had associated nephrolithiasis. These findings indicate screening of cystinuria in patients with isolated idiopathic hematuria without urologic complications.

Hypocitraturia was the most frequent abnormality in 60% of the study patients and more common in children younger than 5 years. Similarly, it was the most common metabolic abnormality in 52% of pediatric kidney stone formers in the study by Tefekli et al. [17] and accounted the second most frequent metabolic disturbance in 31.7% of children in the other report [1]. Urine citrate was significantly lower in patients with nephrolithiasis than in the healthy control group in the study by Batinic et al. [18] and in one of the authors' previous report [19].

Magnesium is an important inhibitor of crystallization and stone formation in normal urine. More than 50% of the study patients had *hypomagnesuria* with normal serum magnesium level.

Up to this research, this is one of the largest cohort studies of children with idiopathic hematuria. It was showed that decreased urinary inhibitor concentration followed by increased promoter excretion were the potential reversible causes of idiopathic hematuria in children. However, a lot of the study patients had both etiologies simultaneously. Therefore, measurement of urine biochemical excretion is highly recommended in patients with isolated idiopathic hematuria, unexplained abdominal pain, recurrent urinary tract infection, dysuria, and familial history of nephrolithiasis to prevent unnecessary invasive diagnostic procedures. As a limitation of this study, it is highly suggested to investigate therapeutic effect of potassium citrate supplements for prevention of

future stone formation in children with idiopathic hematuria. In addition, it is suggested to perform this study in different populations to identify the correlation between cultural variables, urinary metabolic abnormality, and idiopathic hematuria.

Author statements

Ethical approval

The local ethics committee approved this study.

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Competing interests

None declared.

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