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Non-Calculus Signs and Symptoms of Hyperoxaluria and Hyperuricosuria in Children: A Single Experience

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Abstract

Background and Aims: Non-calculus presentations of hyperoxaluria (HX) and Hyperuricosuria (HU) are not common. The aim of this study was to investigate the relationship of symptomatic non-calculus idiopathic HX, HU and both of them with dysuria, failure to thrive (FTT), recurrent urinary tract infection (UTI), dysmorphic red blood cells (RBCs) and abdominal pain in children.

Methods: A cross sectional study was done on 58 children who were aged less than 14 years with history of persistent microscopic or macroscopic hematuria with HX and/or HU, regardless of having renal calculi, between October 2007 and October 2008. The patients were divided into three groups according to the type of crystalluria (I, 10 HX; II, 20 HU; and III, 28 HX+HU).

Results: The common presenting symptoms were abdominal pain (63%) and dysuria (45%). FTT frequently occurred in female (68%). No significant relation was seen between the groups in terms of gender, macroscopic hematuria and recurrent UTI. We found that dysuria, positive family history, FTT, abdominal pain and dysmorphic RBCs in patients with HX were higher when compared to HU group. Moreover, logistic regression analysis showed the higher odds ratio of FTT, abdominal pain and dysmorphic RBCs in patients with HX+HU group when compared to patients with HU.

***Conclusions*:** Although our study showed that non-calculus symptoms and signs of crystalluria such as dysmorphic RBCs, FTT, abdominal pain and dysuria are frequently seen in children with HX, however, further studies are needed.

Keywords: Hyperoxaluria, Hyperuricosuria, Non-Calculus Signs and Symptoms

Introduction

Urolithiasis in children is a relatively infrequent problem (1, 2). There are some known and unknown factors that may cause formation of urinary tract stones (3). Hyperuricosuria (HU) and hyperoxaluria (HX) are two important metabolic risk factors in urolithiasis among pediatric patients. HU has been reported in 2% to 10% of children and adolescents with metabolic predisposition to renal stone formation (4). Simple uric acid stones are uncommon in childhood and often mixed with HX (5). Signs and symptoms of primary HX type I, occurred roughly 1 in 120,000 live births, include nephrocalcinosis (91%) with or without nephrolithiasis, urinary tract infection (UTI) (21%), failure to thrive (FTT) (22%) and uremia (14%) (6). Interestingly, the clinical presentation in

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the early childhood is more likely to be recurrent UTI or enuresis.

Furthermore, the symptoms and signs of HU and HX in those whom a urinary calculus is not detected consist of recurrent abdominal pain (RAP), microscopic and gross hematuria, dysuria and FTT (7). In addition, recurrent UTI and urinary frequency-urgency syndrome can be seen in these patients without renal stones (8).

The aim of our study was to appraise the clinical features and natural history in children with HX and/or HU, especially non-calculus presentations, as well as recurrent UTI.

Materials and Methods

The current cross sectional study was done among 58 patients with history of hematuria with HX and/or HU, regardless of having renal calculi, referred to our pediatric nephrology clinic between October 2007 and October 2008. Inclusion criteria were age less than 14 years, and persistent microscopic or macroscopic hematuria with HX and/or HU. Exclusion criteria were hematuria due to false positive results (occurred with alkaline urine with a pH greater 9 or contamination with oxidizing agents used to clean the perineum), glomerular disease, tumor, trauma, hypercalciuria and unknown causes. The patients were divided into three groups according to the type of crystalluria (I, 10 HX; II, 20 HU; and III, 28 HX+HU). All the patients were examined by one pediatric nephrologist. Moreover, urine analyses and cultures were initially performed for ruling out HX due to UTI. The data was gathered by a special checklist consisting of the demographic (age, sex, weight and height), clinical and paraclinical variables (Table 1).

Table 2 shows the definition of microscopic hematuria, FTT, HU and HX using in the current study.

Statistics:

Data were analyzed using the SPSS, version 15.0. All continuous variables were expressed as mean (±SD). Comparison of all groups in terms of age, sex, FTT, renal stone, recurrent UTI, dysmorphic RBCs were assessed by Chi square and Fisher exact tests. Logistic regression analysis was also used to examine relationships between variables. The P value of less than 0.05 was

Table 1. Physical exam, clinical and paraclinical characteristics in patients

1. History
2. Physical Examination
   a) Check BP, weight and length (body mass index)
   b) Precise skin examination (history of trauma)
   c) Assessment for edema and recent weight gain
   d) Direct visualization of genitals
      Looking for: - Penile urethral meatal erosion
                   - Female introitus pathology
   e) Evaluation for abdominal discomfort or mass
3. Urine Analysis
   a) Regular urinalysis including PH and microscopic examination
   b) Urine culture and sensitivity suspected concomitant UTI
   c) Timed-urine 24 hours for total volume, creatinine, calcium, oxalate, uric acid, protein
   d) Distinguishing dysmorphic RBCs in fresh urine by phase contrast microscopy by one expert person
4. Blood
   a) CBC
   b) BUN, Creatinine, Electrolyte (Calcium, Sodium, Potassium,
Phosphors, Alkaline Phosphotase), Uric acid, C3, C4, CH5o, Anti ds DNA, ANA
5. Radiographic studies
   a) Sonography with special probe: 3.5, 7.5 MHtz (Toshiba Italia with same operator with a high resolution)
   b) CT Scan if needed
   c) Plain X-Ray (KUB) in patients with renal stoned)
   d) VCUG: If any abnormality was detected in sonography such as hydronephrosis, especially in recurrent UTI.
6. Stone analysis in patients with urolithiasis

BP, Blood Pressure; **UTI**, Urinary Tract Infection; **RBCs**, Red Blood Cells; **CBC**, Complete Blood Count; **BUN**, Blood Urea Nitrogen; **MHtz**, Mega Hertz; **CT**, Computed Tumogheraphy; **KUB**, Kidney-Ureter-Bladder; **ESWL**, Extra-Shock Wave Lithotripsy; **VCUG**, Voiding Cysto-Uretrography.

Table 2. Description of persistent microscopic hematuria, FTT, HU, HX and recurrent UTI

Clinical Setting	Definition
Persistent microscopic hematuria	More than five red blood cells per high- power field (×40) in three consecutive monthly urine samples (16).
FTT	Having a weight that is below the 3rd or 5th percentile for their age and a declining growth velocity (i.e. they are not gaining weight as expected) and/or a shift downward in their growth percentiles, crossing two or more percentiles on their growth charts (17).
HU:	
Children between 2-15 years old	Urinary excretion of uric acid in timed urine 24 hr ≥ 520±147 mg/1.73 m^2/day (18).
Children with under 2 years old	Urinary uric acid excretion ≥ 11mg/kg/24hr (19).
HX	
Children older than 3 years old	Urinary oxalate excretion ≥ 36.9±13.7m^2 /day in timed urine 24 hours
Children younger than 3 years old	Urinary oxalate excretion ≥ 0.5mg/kg in 24 hours urine (20).
Recurrent UTI	2 =< UTI in 6 month or 3 =< UTI in 1 year(18).

FTT, Failure to Thrive; **UTI**, Urinary Tract Infection; **hr**, hour; **mg**, milligram; **m^2**, square meter; **kg**, kilogram.

considered as statistically significant.

Results

During one year, fifty-eight patients (31 boys and 27 girls) enrolled into our study with the mean age of 48.2 ± 45.1 weeks. Twenty-six (45%) of our patients were infants under two years of age. The common presenting symptoms were abdominal pain (63%) and dysuria (45%). Renal stones were seen in 26 children. FTT frequently occurred in female patients (68%). Majority of patients with HU (89%) had no dysmorphic RBCs in fresh urine. On the other hand, dysmorphic RBCs were commonly observed in HX and HX-HU groups (Table 3).

No significant relation was seen between the groups in terms of gender, macroscopic hematuria and recurrent UTI. We found that dysuria, positive family history, FTT, abdominal pain and dysmorphic RBCs in patients with HX were higher when compared to HU group (Table 3). Importantly, odds ratio of variables studied was higher in patients with HX and mixed groups when compared to individuals with HU (Table 4).

Discussion

In current study, we found no significant difference in the prevalence of HX, HU and both of them between male and female (P = 0.24). Previous study by Patel *et al* have also reported no association between HX and gender (9) Dysuria without UTI was one of the most common symptoms in our patients, especially in those with HX and HX+ HU (P=0.04). Moreover, logistic regression analysis showed that odds ratio of dysuria, RAP, FTT and dysmorphic RBCs in HX and HX+HU groups are significantly higher than individuals with HU (Table 4). In addition, a family history of urolithiasis was present in 27 children (46%); it was only a major risk factor for patients with HX (Table 4).

RAP is other symptom of non-calculus in our patients especially in HX group. Eight of the ten children in this class have RAP (P<0.0001). The

Table 3. Cross–classification of groups (HU, HX, HU&Hx) by sex, dysuria, family history, hematuria, FTT, abdominal pain, recurrent UTI, dysmorphic, RBC and relation between them.

Variables	HU	HX	HX with HU	P Value
Gender (male/female)	11/9	3/7	17/11	0.24*
Dysuria	5 (25%)	4 (40%)	17 (61%)	0.04*
Family history (+)	6 (30%)	10 (100%)	14 (50%)	0.001*
Macroscopic hematuria	3 (15%)	2 (20%)	7 (25%)	0.8**
FTT	5 (25%)	6 (60%)	17 (61%)	0.04*
Abdominal pain	5 (25%)	8 (80%)	24 (86%)	<0.0001*
Recurrent UTI	5 (25%)	-	11 (39%)	0.06*
Dysmorphic RBC	2 (10%)	7 (70%)	19 (68%)	<0.0001*

HX, hyperoxaluria; **HU**, Hyperuricosuria; **FTT**, Failure to Thrive; **UTI**, Urinary Tract Infection.
*Chi – square test
**Fisher exact test

Table 4: Results from logistic regression analysis of the association between groups (HU, HX, HX & HU)

Variables		HU	HX	HX with HU
Dysuria	OR (95% CI)	1	2 (0.38-10.2)	4.7 (1.3-16)
	P value	-	0.4	0.01
Family history	OR (95% CI)	1	23.3 (3.4-161)	2.3 (0.69-7.8)
	P value	-	0.001	0.2
FTT	OR (95% CI)	1	4.5 (0.9-22)	4.7 (1.3-16)
	P value	-	0.06	0.01
Abdominal pain	OR (95% CI)	1	12 (2.13-67.5)	18 (4.6-69.4)
	P value	-	0.004	<0.0001
Dysmorphic RBC	OR (95% CI)	1	21 (3.5-126)	19 (4.4-82)
	P value	-	0.0007	0.0001

HX, hyperoxaluria; **HU**, Hyperuricosuria; **FTT**, Failure to Thrive; **OR**, Odds Ratio; **CI,** Confidence Interval.

causes of RAP in children are multiple and it has been reported that in approximately 90% of children it is non-organic (10, 11). In another study (12) 42% patients with idiopathic hypercalciuria also had RAP or flank pain. In our experience 56.8% patients without hypercalciuria had RAP; it seems that HX and HU are also the causes of RAP. We suggest that in patients with undiagnosed abdominal pain and UTI, urinary excretion of oxalate and calcium per day should be done to rule out pure HX or its association with hypercalciuria.

Recurrent UTI was seen in 16 cases (27%) of our patients. Interestingly, it did not occur in individuals with HX (P=0.06). It is previously reported that only hypercalciuria and hypocitraturia are the important risk factors for recurrent UTI in crystalluria, similar to our observation (13). Moreover, in a series of 124 children with hypercalciuria reported by Vachvanichsanong *et al* (14) the presenting finding in the younger child is more likely to be recurrent UTI or enuresis. In the same study, fifty patients had UTI and incidence of recurrent UTI was high (39 cases, 78%).

Phase - contrast microscopy is a simple, noninvasive and reliable diagnostic test for urinary dysmorphic RBCs. Although RBC casts and dysmorphic RBCs are strongly suggestive of renal parenchymal diseases, in our experience dysmorphic RBC in patients without renal stone or glomerular disease was frequently observed in HX and HX with HU groups.

FTT was seen in patients with HX and HX +HU more than HU group, especially in girls. It has also been reported that FTT is observed in children with primary hyperoxaluria type 1(15).

Conclusions:

We conclude that non-calculus symptoms and signs of crystalluria such as dysmorphic RBCs, FTT, abdominal pain and dysuria are frequently seen in children with HX. Further studies are required to investigate the differences, implications and better treatment options between these two conditions.

Conslict of interest

None declared.

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