

Idiopathic hypercalciuria in children with urinary tract infection

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ABSTRACT

Introduction. Idiopathic hypercalciuria (IH) predisposes to urinary tract infections (UTIs); however, there is scarce local information regarding such association. Our objectives were to estimate IH prevalence in children with UTI and to assess whether there were differences in relation to the presence or absence of vesicoureteral reflux (VUR). Additionally, the association between IH and salt intake was studied.

Population and Methods. Calciuria was determined in patients younger than 18 years old on whom UTI had been studied (ultrasound and voiding cystourethrogram), and who had no secondary causes of hypercalciuria. IH was defined as a calcium to creatinine ratio of >0.8, 0.6, 0.5 and 0.2 in children aged 0 to 6 months old, 7 to 12 months old, 12 to 24 months old and older than 2 years old, respectively; and a high sodium intake with a urinary sodium to potassium ratio of ≥ 2.5 .

Results. IH prevalence among 136 patients (87 girls, median age: 3 years old) was 20%. Patients with VUR (n= 54) and without VUR (n= 82) had similar characteristics in terms of sex, weight, height, age at diagnosis and age at the time of the study, and clinical features (hematuria, nephrolithiasis, colicky pain, and recurrent UTI), family history of kidney stone formation, and IH prevalence (26% versus 16%, $p= 0.24$). A high sodium intake was more frequently observed in children with hypercalciuria than in those with normal urine calcium levels (76% versus 46%, $p= 0.007$).

Conclusions. IH prevalence in children with UTI was high (20%), with no differences observed between patients with and without VUR. As a recommendation, the presence of IH should be detected in children with UTI, regardless of VUR presence or absence.

Key words: idiopathic hypercalciuria, urinary tract infection, vesicoureteral reflux, children.

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INTRODUCTION

Urinary tract infections (UTIs) are prevalent during childhood in 2%-8% of patients.¹ Since UTIs can lead to permanent kidney damage, it is relevant to identify and provide

treatment for predisposing factors in order to reduce their frequency and, as a result, the associated morbidity.² These include anatomic-functional factors, such as vesicoureteral reflux (VUR) and bladder dysfunction, and metabolic factors, mainly idiopathic hypercalciuria (IH).^{2,3}

IH is a common pediatric disorder (3%-10%)⁴⁻⁶ which predisposes to the development of UTI because the oversaturation of urine with calcium oxalate microcrystals may damage mucous membranes of the urinary tract.⁷ Consequently, different studies have demonstrated an increase in IH prevalence in patients with UTI,^{6,8-13} although some authors have not been able to confirm such association.⁷

The main determining factor of urinary calcium excretion is the concomitant elimination of sodium, which in turn depends on salt intake.¹⁴ In addition, calcium excretion is affected by other extrinsic factors (protein intake, mineral content of water) and intrinsic factors (ethnicity),¹⁵ and this is reflected on the great geographic variability observed in IH prevalence, both in healthy children and in those with UTI.^{6,8-13}

To our knowledge, there are no local data on IH prevalence in children with UTI; for this reason, we conducted this study with two main objectives: 1) to estimate IH prevalence in patients treated for UTI at a children's hospital; and 2) to assess whether such prevalence differs in relation to VUR presence or absence. Additionally, we studied the association between IH and salt intake.

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POPULATION, MATERIAL AND METHODS

Patients

This was a cross-sectional study conducted at the Department of Nephrology of Hospital General de Niños Pedro de Elizalde between December 2012 and December 2013. Patients included were children younger than 18 years old with a history of UTI studied with kidney ultrasound and voiding cystourethrogram (VCUG), with normal blood pressure, arterial blood gases, electrolytes, creatininemia and calcemia.^{16,17} Children were excluded if they had secondary VUR and other urinary tract diseases, required long-term immobilization (hospitalization, bone fracture), had received calcium, vitamin D, systemic corticosteroids and/or diuretics in the past six months prior to the study, or showed signs of endocrinological diseases (short stature, Cushing's syndrome, precocious puberty and hirsutism) and/or of metabolic diseases (hypotonicity, hepatosplenomegaly, mental retardation, seizures, ataxia, or coma).^{6,12,18}

Method

Patients who attended the Department of Nephrology over the study period and who met the inclusion criteria were invited to participate in the protocol. Blood lab tests (arterial blood gases, electrolytes, creatinine, and calcium) and urine tests (calcium, ionogram, and creatinine) mostly coincided with the usual tests requested during a control so as to avoid modifying the rate of follow-ups. During consultation, patients were specifically asked about their family history of kidney stone formation.

Definitions

UTI: single microorganism count $>10^5$ colony forming units (CFU) per mL with urinary tract inflammatory reaction (>10 leukocytes per field and/or presence of pyocytes) in a midstream urine sample collection. Significant counts of 10^4 CFU/mL in urine samples obtained by urethral catheterization and of a single CFU if samples were obtained by suprapubic puncture were also considered.¹⁹

Recurrent UTI: two or more UTI episodes with a sterile urine interval documented in a negative urine culture.²⁰

VUR: diagnosed with a VCUG and classified as grade I-V as per the international classification of VUR.²¹ Patients were grouped as low grade (I

and II) or high grade (III to V); in cases of bilateral VUR, the highest grade was considered for its classification.¹

IH: patients with normal calcemia in absence of conditions or drugs that may cause hypercalciuria,^{6,12,18} with a calcium to creatinine ratio of >0.8 in children aged 0 to 6 months old, >0.6 in children aged 7 to 12 months old, >0.5 in children aged 12 to 24 months old and >0.2 in children older than 2 years old measured using a fasting urine sample.^{15,22,23}

The calcium to creatinine ratio was used in an isolated urine sample to estimate calcium excretion because it shows an adequate correlation with a 24-hour urine collection,²⁴ it can be done in children who have neither bladder nor bowel control, and also because there is more pediatric information on normal urinary calcium values for this ratio than for the 24-hour urine collection.¹⁵ Although it has been reported that calciuria measured in a fasting second morning void sample is more representative than the 24-hour urine collection,²⁵ we decided to use the first morning void sample because it has been widely accepted in the literature,^{6,9-13,20} especially taking into account how difficult it may be to keep infants fasting until their second void.

Spontaneous sodium intake was estimated based on urinary output. As per urinary ionogram results, patients were classified into two groups: a group with a low sodium intake (sodium to potassium ratio ≤ 2.4) and another one with a high sodium intake (sodium to potassium ratio ≥ 2.5).⁴

Urine and plasma creatinine levels were determined using the Jaffé kinetic method; urine calcium was determined using spectrometry; and the urinary ionogram was performed with a flame photometer.

The following data were collected: sex, age at the time of the study, age at diagnosis, weight, height, clinical signs (presence of hematuria, nephrolithiasis, episodes of colicky pain, and number of UTIs), history of lithiasis in first-degree relatives. Ultrasound and VCUG findings were also recorded. Lastly, the presence of IH and salt intake were also recorded.

Ethical considerations: The study was approved by the Research Committee and the Ethics Committee of our hospital. Patients were included once their parents had signed an informed consent. An assent was obtained from children older than 12 years old.

Statistical analysis

Given that IH prevalence in healthy children may reach up to 10%⁴⁻⁶ of the population and considering a 95% confidence interval and a power of 80%, it was estimated that 136 subjects should be included in the study. This sample size also proved sufficient to establish objective differences in the prevalence of IH between patients with and without VUR because, based on an IH prevalence of 20% in patients without VUR and of 58% in patients with VUR,^{9,12} and considering a 1:1 ratio between patients with and without VUR, a power of 80% and a 95% confidence interval, 26 patients had to be included per group.

Patients were classified based on VUR presence or absence. Clinical and demographic characteristics and lab parameters were analyzed descriptively. Continuous outcome measures had a non-parametric distribution (Shapiro-Wilk's test), so they were expressed as a median (range), while categorical outcome measures were expressed as an occurrence rate and percentage. Comparisons between groups were done using the Wilcoxon test, the chi-square test² or Fisher's exact test, as applicable. The Statistix software, version 7 (IBM version; Analytical Software, Tallahassee, FL) was used, and a $p < 0.05$ was considered significant.

RESULTS

One hundred and thirty-six patients were included; their median age was 3 years old (0,16-18); 87 (64%) were girls; and IH prevalence was 20% (27 patients). VUR was diagnosed in

54 (39.7%) patients, half of the cases showed bilaterality and 21 (38.9%) patients had a high grade VUR. Patients were divided according to VUR presence (n= 54) or absence (n= 82). Both groups had similar demographic characteristics (sex, age at the time of the study, age at diagnosis, weight, and height) and clinical signs (presence of hematuria, nephrolithiasis, episodes of colicky pain, and recurrent UTI).

In addition, no differences were observed in relation to the rate of kidney ultrasounds with positive findings, family history of lithiasis, spontaneous sodium intake, or IH prevalence (26% in patients with VUR versus 16% in patients without VUR, $p = 0.24$). Table 1 shows the details of such findings. In addition, no significant differences were observed in IH prevalence between patients with unilateral or bilateral VUR (29.6% versus 22.2%, $p = 0.53$) nor between low grade and high grade VUR (27.2% versus 23,8%, $p = 1.00$). We also noted that IH presence was significantly associated with recurrent UTI ($p = 0.02$), but only in patients without VUR (Table 2).

Additionally, we studied if there was an association between IH and salt intake. A high sodium intake was more commonly observed in patients with hypercalciuria than in those with normal urine calcium levels (76% versus 46%, $p = 0.007$). When considering the overall sample categorized as per recurrent or non-recurrent UTI and as per the presence or absence of VUR, a statistically significant association was observed

TABLE 1. General characteristics of patients with and without vesicoureteral reflux

Characteristic	Children without VUR (n= 82)	Children with VUR (n= 54)	p value
Sex (female)	54	33	0.57
Age at diagnosis (years old)	1.5 (0.16-15)	1 (0.08-11)	0.53
Age at the time of the study (years old)	2.58 (0.16-15.5)	3 (0.5-18)	0.57
Weight (kg)	13.8 (4.32-63.5)	13.21 (6-60)	0.98
Hematuria	12 (14.6%)	5 (9.2%)	0.43
Kidney colic	4 (4.8%)	5 (9.2%)	0.48
Nephrolithiasis	2 (2.5%)	-	0.51
Family history of lithiasis*	3/67 (4.5%)	0/46 (0%)	0.26
Pathological kidney ultrasound	38 (46.3%)	21 (38.8%)	0.39
Recurrent urinary tract infection*	41/79 (51.9%)	27/50 (54%)	0.81
Hypercalciuria	13 (16%)	14 (26%)	0.24
High sodium intake*	40/75 (53.3%)	25/50 (50%)	0.71

VUR: vesicoureteral reflux.

Data expressed as a median or frequency of distribution, with the range or percentage between brackets, respectively.

Outcome measures marked with (*) indicate positive data regarding the number of available data for each patient group.

between sodium intake and IH only in the group of children with recurrent UTI ($p=0.03$) (Table 3). Lastly, no significant differences were observed between patients with and without IH in terms of presence of hematuria (5 versus 12, $p=0.33$), episodes of colicky pain (4 versus 5, $p=0.07$), kidney stones (0 versus 2, $p=1.00$), or family history of lithiasis in first-degree relatives (0 versus 2, $p=1.00$).

DISCUSSION

The main finding of this study is the high prevalence of IH (20%) in children with UTI. As mentioned above, there are several factors that have an impact on urinary calcium excretion and lead to a high geographic variability in IH prevalence in asymptomatic children.¹⁵ For example, in Eastern Europe countries, IH prevalence ranges between 3% and 7%; while in other countries it is as follows: Spain: 3.8%, Germany: 8.6%, Italy: 9.1%; United States of America: 10%, Japan: 0.6%, and Brazil: 3.2%.^{6,9,15,18,26-29} Moreover, such variability has

been observed among different regions in the same country. For example, four Iranian studies reported that IH prevalence was 0.2%, 3.6%, 11.4%, and 13.3%, respectively.^{8,7,10,13} More interestingly, in Argentina, Alconcher, et al.³⁰ studied 220 healthy school children and found 28 cases (12.7%) with a urinary calcium excretion level higher than the globally accepted cut-off value (4 mg/kg/day);^{22,23} however, in relation to the upper limit observed in their own patients (4.74 mg/kg/day), only 12 (5.5%) had IH.

In spite of the differences observed depending on the origin of the study, most publications have reported that IH prevalence in children with UTI is significantly higher (21%-43%) than in asymptomatic children.^{6,8-10}

Considering that IH prevalence reported by Alconcher³⁰ in Argentine children was 5.5%,³⁰ IH prevalence in our patients with UTI is almost four times higher (20%). In turn, the value found in our patients is also higher than that reported by most studies in healthy children. Based on this, it is possible to infer that IH rate among children

TABLE 2. Association between idiopathic hypercalciuria and frequency of urinary tract infections in patients with and without vesicoureteral reflux

Characteristic	First-time urinary tract infection (n= 61)	Recurrent urinary tract infection (n= 68)	p value
Without vesicoureteral reflux	n= 38	n= 41	
Without idiopathic hypercalciuria	36	31	0.02
With idiopathic hypercalciuria	2	10	
With vesicoureteral reflux	n= 23	n= 27	
Without idiopathic hypercalciuria	17	21	1.00
With idiopathic hypercalciuria	6	6	

TABLE 3. Association between the presence of idiopathic hypercalciuria and urinary tract infection in children in terms of sodium intake

Condition	Low sodium intake		High sodium intake		p value
	Normal urinary calcium level	Hypercalciuria	Normal urinary calcium level	Hypercalciuria	
First-time UTI (n= 56)	30	4	19	3	1.00
Recurrent UTI (n= 62)	22	2	25	13	0.03
Without VUR (n= 75)	32	3	30	10	0.07
With VUR (n= 50)	22	3	16	9	0.09

UTI: urinary tract infection; VUR: vesicoureteral reflux.

included in our study is higher than in the general population.^{6,9,15,18,26-29}

Besides, IH prevalence in children with VUR had been previously studied because VUR prevalence among children with kidney stones (4%-8%)³¹ is higher than in the healthy population (<1%)³². García Nieto described a very high rate (58.6%) of IH compared to the general population of his country.¹² Other studies reported a higher prevalence of IH in patients with VUR, although at a lower rate (17%-21%).^{7,13} Similarly, our patients with VUR showed a high IH prevalence, but with no significant differences when compared to patients without VUR (26% versus 16%, respectively, $p=0.24$). This finding is consistent with what has been reported by Biyikli.⁶ However, it should be noted that in both Biyikli's study and in our study, IH prevalence in both groups was high reflecting a high rate of this condition in children with UTI, regardless of the presence or absence of an associated urological malformation. In turn, and in accordance with what has been observed by García Nieto, the presence of IH in our series was not related to VUR grade nor unilaterality or bilaterality.¹² In contrast, although Madani, et al. did not observe an association between IH and the presence of unilateral or bilateral VUR, they found a significant association between IH and grade I VUR.¹³

The presence of IH has been previously associated with recurrent UTI. Stojanovi observed an increase in IH prevalence from 21% in patients with first-time UTI to 44% in those with recurrent UTI;⁹ at the same time, Biyikli reported a prevalence of 43% in children with this condition.⁶ We also observed such association in our patients; however, it was only objectively confirmed in patients without VUR. Since patients previously diagnosed with VUR were, at the time of the study, aware of the corresponding related hygienic and dietary measures (to prevent constipation and urinary retention), and given that many of them were also receiving antibiotic chemoprophylaxis, it could be estimated that these factors may have contributed to reduce the number of UTI observed in this group. The other clinical manifestations attributed to IH (hematuria, colicky pain, and kidney stones) were similar to what has been reported by other authors.⁶ IH-related potential bone mass reduction⁴ was not studied in our patients.

Finally, given that there is a positive linear relation between sodium and calcium urinary

excretion, both in healthy children as well as in patients with IH,^{4,33} we analyzed if there was an association between IH and spontaneous salt intake. It is worth noting that 76% of patients with IH showed a high salt intake when compared to 46% of children with normal urine calcium levels. Although the urinary sodium to potassium ratio allows to indirectly estimate recent salt intake,⁴ and since no dietary recommendations were given to our patients at the time of the study, such ratio may be a reflection of their usual salt intake. In a secondary analysis, patients were classified as per having first-time UTI or recurrent UTI, and as per the presence or absence of VUR. We observed that the association between a high salt intake and IH was only present in children with recurrent UTI (*Table 3*). The usual treatment for IH includes dietary salt and protein restriction and an increased fluid and potassium intake, or the addition of potassium citrate and/or hydrochlorothiazide when dietary treatment fails.⁴ Based on this treatment, López observed in 59 children with hypercalciuria and recurrent UTI that achieving a normal calcium excretion prevented the recurrence of a new UTI in 95% of cases.²⁰ Similarly, Liern, et al. treated 46 children with hypercalciuria and achieved an improvement of associated symptoms, including recurrent UTI, in most cases.³⁴

Our study has some limitations which should be taken into account. When comparing IH prevalence in our patients to a prior population study conducted in a different region of Argentina,³⁰ it cannot be assured that there are no differences between both groups in terms of prevalence measured by extrinsic factors, such as the type of diet or water mineral content, among others. However, IH prevalence among our patients is clearly higher than that described for asymptomatic children worldwide.^{6-10,15,26-29} Also, in contrast to previous studies,^{12,35} the prevalence of a family history of lithiasis in patients with hypercalciuria was extremely uncommon. This may be due to the fact that search was restricted to first-degree relatives; still, 20% of patients reported that they were unaware of such information. In addition, such under-recording may have been due to the unawareness of lithiasis symptoms, which may be non-specific and/or mild. However, it should be mentioned that, in the study conducted with Argentine children, no significant differences were observed between patients with and without a family history of lithiasis in terms of calcium excretion.³⁰

This study contributes local data on the association between IH and UTI resulting in the following conclusions: 1) IH prevalence in children with UTI was high (20%); 2) although no significant differences were observed in IH prevalence between patients with (26%) and without VUR (16%), it was high in both groups; and 3) a high salt intake was more commonly observed in children with hypercalciuria. Based on these findings, and as a recommendation, IH presence should be detected in children with UTI, regardless of VUR presence or absence. ■

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