



ORIGINAL ARTICLE

A family history of renal lithiasis in children diagnosed of urinary tract infection by *Escherichia coli*[☆]

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KEYWORDS

Urinary tract infections;
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Abstract

Introduction: Urinary tract infections (UTI) caused by *Escherichia coli* (*E. coli*) are common in patients with idiopathic hypercalciuria. As both UTI and hypercalciuria (prelithiasis) have a genetic basis, we wanted to know whether the family history of urolithiasis is more common in children with UTIs caused by *E. coli*. Secondly, we wondered if the renal scars are more common in children with prelithiasis.

Material and methods: Ambispective study with collected data from 104 patients (40 male, 64 female) followed after having been diagnosed of UTI by *E. coli* at least once. These patients were asked about the existence of urolithiasis in relatives. The calcium and citrate urinary elimination was quantified in 80 children.

Results: In the total sample, family history was positive for urolithiasis in a significantly higher frequency in those children ($n=71$; 68.3%) than in the control population in our area (29.7%; previously published data). Prelithiasis frequency in children with UTI was 47.5% (38/80). An association was observed between the diagnosis of prelithiasis both with family history of urolithiasis ($p=0.030$) and the diagnosis of vesicoureteral reflux ($p=0.034$). Children who developed renal scarring had an increased risk of prelithiasis (OR 5.3; $p=0.033$).

Conclusions: The frequency of family history of urolithiasis in children with UTI caused by *E. coli* is very high. Based on our results we hypothesize that the predisposition to lithiasis can involve a constitutively altered defense to *E. coli* and, therefore, a greater possibility for renal scars.

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PALABRAS CLAVE

Infecciones de la vía urinaria;
 Hipercalciuria;
 Historia familiar;
Escherichia coli

Historia familiar de litiasis renal en pacientes diagnosticados de infección del tracto urinario por *Escherichia coli*

Resumen

Introducción: Las infecciones de la vía urinaria (IVU) causadas por *Escherichia coli* (*E. coli*) son frecuentes en pacientes con hipercalciuria idiopática. Al ser tanto IVU como hipercalciuria (prelitisias) de origen genético, planteamos si la historia familiar de urolitiasis es más frecuente en niños con IVU causada por *E. coli*. Secundariamente, planteamos si las cicatrices renales son más frecuentes en niños con prelitiasis.

Material y métodos: Estudio ambispectivo con datos de 104 pacientes (40 masculinos y 64 femeninos) seguidos tras haber sido diagnosticados, al menos una vez, de IVU por *E. coli*. Se preguntó por la existencia de urolitiasis en familiares (primer y segundo grado). En 80 pacientes se determinó la eliminación urinaria de calcio y citrato.

Resultados: En toda la muestra, la historia familiar de urolitiasis fue positiva en una frecuencia significativamente mayor de estos niños ($n = 71$; 68,3%) que en la población de control del mismo área (el 29,7% según datos previos publicados). La frecuencia de prelitiasis en niños con IVU fue del 47,5% (38/80). Se observó asociación entre prelitiasis tanto con la historia familiar de urolitiasis ($p = 0,030$) como con el reflujo vesicoureteral ($p = 0,034$). Además, los pacientes que desarrollaron cicatrices renales tenían más prelitiasis (OR 5,3; $p = 0,033$).

Conclusiones: La frecuencia de historia familiar de urolitiasis en niños con IVU causada por *E. coli* es muy alta. Basándonos en nuestros resultados, sugerimos la hipótesis de que la predisposición a litiasis involucra una defensa alterada contra *E. coli* y, consecuentemente, una mayor posibilidad de cicatrices renales.

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Introduction

Urinary tract infection (UTI) is one of the most common causes of bacterial infection in children. Various agents are involved in its cause,¹ although predisposing genetic factor play each time a larger role. In certain families are UTIs, especially those caused by *Escherichia coli* (*E. coli*), more frequent in members of successive generations.²

Moreover, idiopathic hypercalciuria (IH) and hypocitraturia, are the most common cause of kidney stones in both adult and pediatric patients.³ For the same reason, they are also the most common metabolic anomalies observed in children who, without having eliminated kidney stones yet, have genetic predisposition to develop them.^{4,5} This situation, though not specific to the pediatric age, is known as prelitiasis.⁶ One of the earliest forms of clinical manifestation in children with prelitiasis is in the form of UTI.^{7,8}

As both conditions, UTIs and prelitiasis, have a genetic basis, we wanted to know whether the family history of urolithiasis in relatives is more common in children diagnosed with UTIs caused by *E. coli*. Furthermore, a secondary objective was to look whether this condition is related with renal scar and vesicoureteral reflux (VUR). This paper is unprecedented in the medical literature.

Methods**Participants**

Ambispective study with data collected from 104 patients (40 male, 64 female) from Pediatric Nephrology Outpatients followed in our hospital after being diagnosed of UTI or

asymptomatic bacteriuria (ABU) by *E. coli*. UTI was defined by a positive urine culture with compatible clinical and complementary tests. The recruitment period was between November 2014 and February 2015. As control group was used a cohort publishes before from the same population.⁹

Procedure

All patients underwent renal and urinary tract ultrasound after the first UTI. Other complementary studies were performed depending on the individual characteristics of each patient.

During the clinical interview, every patient was asked about family history of urolithiasis in first and second degree relatives.

Vesicoureteral reflux was diagnosed by cistosonography. Renal scars were detected in renal scintigraphy by dimer-captosuccinic acid (DMSA). Both test were done following both hospital and national guidelines.^{10,11}

Calcium, citrate and creatinine concentrations were determined in an isolated urine sample not fasting (usually the second in the day). This was possible to perform in 80 patients and calcium/creatinine, citrate/creatinine and calcium/citrate ratios were calculated. The urine sample was collected at least one month after the last UTI.

Definitions and analytical procedures

Hypercalciuria was defined as the ratio urinary calcium/creatinine was elevated (>0.8 mg/mg in under six months,¹² >0.6 mg/mg between six and 12 months,¹² >0.47 mg/mg between one and two years,¹³ >0.28 mg/mg

from two to four years¹⁴ and >0.20 mg/mg in over four years^{15,16}).

It was considered hypocitraturia when citrate/creatinine ratio was less than 180 mg/g.¹⁷ Lithogenic risk was deemed when calcium/citrate ratio was above 0.33 mg/mg.¹⁷

Based on these data it was considered that a child has prelithiasis when there is hypercalciuria and/or hypocitraturia and/or lithogenic risk.

Calcium was measured by photometric assay, creatinine was determined by the creatininase method (Roche/Hitachi Cobas c 701/702) and urinary citrate was assessed by the citrate lyase method (917 Roche/Hitachi; Roche Diagnostics).

Data analysis

Basic statistics and chi-square test with Yates correction was conducted, when necessary. Parsimonious multivariate logistic regression models were fitted to identify variables associated with prelithiasis. *p*-Values were two-tailed; statistical significance was considered attained when *p* < 0.05. Statistical analysis was performed with the SPSS for Windows version 24 software package.

Ethical aspects

The study was conducted according to the principles of the Declaration of Helsinki. All of the procedures and protocols followed during this study meet the ethical, administrative, and data protection requirements imposed by the Paediatrics Service of our hospital, which are established in accordance with the law of Spain. All parents gave informed consent.

Results

The age at diagnosis of the first UTI or ABU was 20.8 ± 31.4 months (range 0.1–132.4 months). 54.8% (*n* = 57) of patients suffered a single pyelonephritis and a further 2.9% (*n* = 3), several pyelonephritis. A single episode of acute cystitis was diagnosed in 4.8% (*n* = 5) of patients and 16.3% (*n* = 17) suffered several episodes. 6.7% (*n* = 7) of patients had been diagnosed with ABU. Lastly, two patients (1.9%) suffered sepsis of urologic origin and in 13 cases (12.5%) the location of the infection in the urine tract could not be properly determined.

Vesicoureteral reflux (VUR) was diagnosed in 21/53 children who underwent a cistosonography. Renal scars were observed in 26/66 patients who underwent a DMSA.

Hypercalciuria was detected in 10/80 cases (12.5%), hypocitraturia in 4/80 (5%) and high calcium/citrate ratio in 28/80 (35%). In total, prelithiasis was found in 38/80 patients (47.5%).

Family history of urolithiasis was established in a total of 71/104 families (68.3%) [22 of first degree (21.2%), 41 of second degree (39.4%) and eight in both degrees (7.7%)].

A relationship was observed with prelithiasis in children with UTI history with a family history of urolithiasis (Table 1) (Odds ratio: 2.93; 95% CI: 1.12–7.67; *p* = 0.03). Table 2 shows

Table 1 Association between diagnosis of prelithiasis in patients with UTI and a family history of urolithiasis (*n* = 80) (*p* = 0.03).

	Family history of urolithiasis	Absence of family history of urolithiasis
Prelithiasis	29	9
Absence of prelithiasis	22	20

the risk of prelithiasis in the cases with renal scar that was 5.3 (*p* = 0.033) and 5.2 in the cases with VUR (*p* = 0.034).

Discussion

To confirm the connection between the two entities, we studied in this paper the frequency of family history of urolithiasis in a large group of children diagnosed with UTI caused by *E. coli*. To avoid difficulties of interpretation, we discarded children that were diagnosed with UTI caused by *Proteus* or other urease-carrying bacteria. In addition, only children with UTI caused by *E. coli* were selected because of the susceptibility factors that have been recently verified with molecular biology techniques which have been studied in this type of bacteria.^{18,19} Patients with ABU were considered too because it has been described a connection with UTI either before or after this diagnosis.^{20,21}

The frequency of family history of urolithiasis in our series (68.3%) is much higher than previously described by us in our control population average (28.1%).⁹ In this regard, as seems reasonable, an association between the presence of prelithiasis in children with UTI and family history of urolithiasis was observed (Table 1). Although the use of a historical cohort can be considered as a methodological limitation, the population in this group is relative homogenous due to insularity.

Two different pathogenic sequences for the relationship between UTI and nephrolithiasis have been classically recognized. The first is that in which the UTI would be primary and the stone formation a secondary consequence (*infection-induced stones*). In the other is the formation of stones and UTI two separate entities (*infection-associated stones*).

Regarding the first option, Hagar and McGrath suggested in 1925 that urease was involved in the biochemical basis of the formation of kidney stones in cases of UTI, especially in those caused by *Proteus*.²² A year later, James B. Sumner purified and isolated urease. This author demonstrated that urease was a protein that catalyzes the hydrolysis of urea.²³ His discovery led to being awarded the Nobel Prize in Chemistry in 1946. Urea lysis induced by urease increases urinary levels of ammonia, bicarbonate and pH. These chemical changes induce urinary supersaturation and promote crystallization of struvite and carbonate apatite, resulting in crystalline genesis. It indicated also that bacteria can remain within the crystals themselves, which could protect the organisms from being dragged by the urine and be more effective in the production of crystals.

Regarding the second option, it has been described that microcrystals of calcium oxalate monohydrate could damage the epithelial cells of urinary tract, altering their

Table 2 Variables associated with diagnosis of prelithiasis through in patients with UTI. Binary logistic multivariate regression models.

	Coeff	Wald	OR	95% CI	p-Value
Renal scarring (presence vs <u>absence</u>)	1.665	4.551	5.286	1.145–24.403	0,033
Vesicoureteral reflux (presence vs <u>absence</u>)	1.567	4.470	5.246	1.129–24.380	0,034
Sex (boy vs <u>girl</u>)	–1.416	3.138	76	0.051–1.163	0,076
Intercept	–991	658	2.267	–	132

Note: The category of every dichotomous variable that has been considered as reference is underlined.

protective role in the urinary tract. Thus, these microcrystals could influence the cellular defense mechanisms as they are attached to urothelial cells and could also be able to activate processes of crystal growth and retention in the renal parenchyma, promoting inflammatory processes and interstitial fibrosis.²⁴ This action would be mediated by glycoproteins and cytokines, which influence the resilience of the urothelial cells²⁵ and therefore favor bacterial invasion.

In recent years, there has been a big step in understanding a narrower association. This time is not between UTIs and stones but between UTIs and prelithiasis, suggesting the existence of common genetic factors. In the 1960s, Antonio Valverde, Spanish urologist located in Córdoba, noted that some children with hypercalciuria had suffered of UTIs.^{26,27} In 1987, Cervera et al. reported that the frequency of UTI in patients with idiopathic hypercalciuria was 48.9%.⁷ This association was confirmed in several subsequent series,^{8,28–31} which contrasts with the frequency of UTI in the control population without hypercalciuria, in which a prevalence was estimated at about 1–2% of boys and 3.5% in girls.³² Similarly and inversely, the frequency series of hypercalciuria in children with UTIs has been described between 20%³³ and 44%.³⁴

The rate of increase in the urinary excretion of calcium in our series is not very high. Perhaps it is because many children were studied at a young age; in many cases, idiopathic hypercalciuria is detected after three or four years of age. In recent times, great importance has been given to the calcium/citrate ratio; a value of this ratio above 0.33 indicates that the urine is potentially lithogenic, irrespective of age and the time of collection.^{17,35,36} The frequency of prelithiasis rises to almost half of the sample (47.5%) if, in addition, we include children with high calcium/citrate and/or hypocitraturia. In our experience we have found that many children with idiopathic hypercalciuria can normalize the urinary calcium excretion in adolescence and at the same time reduce the urinary citrate excretion. We have also observed in the families of some children with idiopathic hypercalciuria, that parents with urolithiasis presented hypocitraturia but with a normal urinary excretion of calcium. It seems as if they were two sides of the same process. Also it described that idiopathic hypercalciuria may be associated with hypocitraturia in the absence of distal renal tubular acidosis.³⁷

The relationship between prelithiasis and renal scarring (Table 2) has not been previously described in the literature as a serious impact with what is mentioned above. The explanation for this association is unknown. As stated before, in recent years there has been a breakthrough in understanding the cause of UTI from the point of view of

the host, mostly thanks to molecular biology. In regard to this, mutations and polymorphisms which benefits UTIs have been described in some genes that encode proteins involved in innate immunity.^{2,3,18,19}

These changes would therefore indicate a lower heritable and defensive ability against certain Gram negative bacteria, especially *E. coli*. It is likely, therefore, that children with prelithiasis are somehow carriers of some of these genetic characteristics which would carry a reduced defense capability against these bacteria^{7,8,26–31} and thus a greater chance of developing renal scars. Further studies to confirm or deny our findings are necessary.

Still to discuss is the relationship between the diagnosis of prelithiasis and the existence of vesicoureteral reflux (Table 2). In 2003, one of us reported that the prevalence of hypercalciuria was higher in pediatric patients with vesicoureteral reflux than in the general population and that urolithiasis in these patients with this malformation probably have a metabolic origin.³⁸ We also described that hypercalciuria appeared to be inherited as an autosomal dominant trait, although it seemed to be more likely to be inherited from the mother.³⁶ Recent publications have confirmed that the frequency of hypercalciuria is higher in pediatric patients with vesicoureteral reflux compared to healthy children, although their families were not studied.³⁹

Conflict of interests

The authors have no conflict of interests to declare.

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References

- Finer G, Landau D. Pathogenesis of urinary tract infections with normal female anatomy. *Lancet Infect Dis.* 2004;4:631–5.
- Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K, Stamm WE. Risk factors for recurrent urinary tract infection in young women. *J Infect Dis.* 2000;182:1177–82.
- Bartosh SM. Medical management of pediatric stone disease. *Urol Clin North Am.* 2004;31:575–87.
- Coe FL, Parks JM, Moore ES. Familial idiopathic hypercalciuria. *N Engl J Med.* 1979;300:337–40.
- Méhes K, Szlid ZS. Autosomal dominant inheritance of hypercalciuria. *Eur J Pediatr.* 1980;133:239–42.
- Jung A, Kamińska A, Olszewski S, Rutka J. A form of premorbid condition of urolithiasis and urinary stone composition in children with urolithiasis. *Pol Merkur Lekarski.* 2000;8:188–90.

7. Cervera A, Corral MJ, Gómez Campdera FJ, de Lecea AM, Luque A, Lopez Gomez JM. Idiopathic hypercalciuria in children. Classification, clinical manifestations and outcome. *Acta Paediatr Scand.* 1987;76:271–8.
8. Vachvanichsanong P, Malagon M, Moore ES. Urinary tract infection in children associated with idiopathic hypercalciuria. *Scand J Urol Nephrol.* 2001;35:112–6.
9. García-Nieto VM, Hernández-González MJ, Luis- Yanes MI, García-Rodríguez VE, Armas-Rodríguez A, Abreu-Yanes I. Does neonatal renal ectasia is a sign of genetic predisposition to suffer from kidney stone in adults? *Pediatr Nephrol.* 2009;24:1852.
10. García Nieto VM, Luis Yanes MI, Arango Sancho P, Sotoca Fernandez JV. Usefulness of basic renal function tests in decision-making in children with loss of renal parenchyma and/or dilation of the urinary tract. *Nefrología.* 2016;36:222–31.
11. Grupo de trabajo de la Guía de Práctica Clínica sobre Infección del Tracto Urinario en la Población Pediátrica. Guía de práctica clínica sobre infección del tracto urinario en la población pediátrica. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad, Política Social e Igualdad. Instituto Aragonés de Ciencias de la Salud; 2011. Guías de Práctica Clínica en el SNS: I+CS No 2009/01.
12. Stapleton FB. Hematuria associated with hypercalciuria and hyperuricosuria: a practical approach. *Pediatr Nephrol.* 1994;8:756–61.
13. Ubalde E, García de Jalón A, Abad A, Loris C. Excreción urinaria de calcio en niños sanos. Estudio colaborativo multicéntrico. *Nefrología.* 1988;8:224–30.
14. So NP, Osorio AV, Simon SD, Alon US. Normal urinary calcium/creatinine ratios in African-American and Caucasian children. *Pediatr Nephrol.* 2001;16:133–9.
15. Butani L, Kalia A. Idiopathic hypercalciuria in children – how valid are the existing diagnostic criteria? *Pediatr Nephrol.* 2004;19:577–82.
16. Melián JS, García-Nieto V, Sosa AM. Herencia y prevalencia de hipercalciuria en la población infantil de la isla de La Gomera. *Nefrología.* 2000;20:510–6.
17. Srivastava T, Winston MJ, Auron A, Alon US. Urine calcium/citrate ratio in children with hypercalciuric stones. *Pediatr Res.* 2009;66:85–90.
18. Svanborg-Eden C, de Man P, Jodal U, Linder H, Lomberg H. Host parasite interaction in urinary tract infection. *Pediatr Nephrol.* 1987;1:623–31.
19. Artifoni L, Negrisolo S, Montini G, Zucchetta P, Molinari PP, Cassar W, et al. Interleukin-8 and CXCR1 receptor functional polymorphisms and susceptibility to acute pyelonephritis. *J Urol.* 2007;177:1102–6.
20. Kunin CM. The natural history of recurrent bacteriuria in school-girls. *N Engl J Med.* 1970;282:1443–8.
21. Savage DC, Wilson MI, McHardy M, Dewar DA, Fee WM. Covert bacteriuria of childhood. A clinical and epidemiological study. *Arch Dis Child.* 1973;48:8–20.
22. Hagar BH, McGrath TB. The etiology of incrustated cystitis with alkaline urine. *JAMA.* 1925;85:1352–5.
23. Sumner JB. Isolation and crystallization of enzyme urease: preliminary paper. *J Biol Chem.* 1926;69:435–41.
24. Hammes M, Lieske JC, Pawar S, Spargo B, Tobback FG. Calcium oxalate monohydrate crystals stimulate gene expression in renal epithelial cells. *Kidney Int.* 1995;48:501–9.
25. Lieske JC, Hammes MS, Hoyer JR, Toback FG. Renal cell osteopontin production is stimulated by calcium oxalate monohydrate crystals. *Kidney Int.* 1997;51:679–86.
26. Valverde A. A propos de lithiase urinaire infantile. *Acta Urol Belg.* 1962;30:568–72.
27. Valverde A. Litiasis metabólica infantil. *Rev Esp Pediatr.* 1967;23:97–101.
28. Heiliczcer J, Canonigo BB, Bishof NA, Moore ES. Non calculi urinary tract disorders secondary to idiopathic hypercalciuria in children. *Pediatr Clin North Am.* 1987;34:711–8.
29. García Nieto V, Muros de Fuentes M, Quintero Quintero M, Gómez de la Rosa JL. Estudio de la clínica de presentación de la hipercalciuria idiopática en la infancia. *Acta Ped Esp.* 1991;49:413–6.
30. Lopez MM, Castillo AL, Chavez BJ, Ramones C. Hypercalciuria and recurrent urinary tract infection in Venezuelan children. *Pediatr Nephrol.* 1999;13:433–7.
31. Escribano J, Balaguer A, Martin R, Feliu A, Espax R. Childhood idiopathic hypercalciuria. *Scand J Urol Nephrol.* 2003;38:422–6.
32. Jodal U, Winberg J. Management of children with unobstructed urinary tract infection. *Pediatr Nephrol.* 1987;1:647–56.
33. Balestracci A, Battaglia LM, Toledo I, Martin SM, Wainsztein RE. Hipercalciuria idiopática en niños con infección del tracto urinario. *Arch Argent Pediatr.* 2014;112:428–33.
34. Stojanović VD, Milosević BO, Djapić MB, Bubalo JD. Idiopathic hypercalciuria associated with urinary tract infection in children. *Pediatr Nephrol.* 2007;22:1291–5.
35. Höbarth K, Hofbauer J. Value of routine citrate analysis and calcium/citrate ratio in calcium urolithiasis. *Eur Urol.* 1991;19:165–8.
36. Grases F, García-Ferragut L, Costa-Bauzá A, Conte A, Garcia-Raja A. Simple test to evaluate the risk of urinary calcium stone formation. *Clin Chim Acta.* 1997;263:43–55.
37. Penido MG, Lima EM, Souto MF, Marino VS, Tupinamba AL, França A. Hypocitraturia: a risk factor for reduced bone mineral density in idiopathic hypercalciuria? *Pediatr Nephrol.* 2006;21:74–8.
38. García-Nieto V, Siverio B, Monge M, Toledo C, Molini N. Urinary calcium excretion in children with vesicoureteral reflux. *Nephrol Dial Transplant.* 2003;18:507–11.
39. Badeli H, Sadeghi M, Shafe O, Khoshnevis T, Heidarzadeh A. Determination and comparison of mean random urine calcium between children with vesicoureteral reflux and those with improved vesicoureteral reflux. *Saudi J Kidney Dis Transpl.* 2011;22:79–82.