To investigate the long-term outcome of the frequency-dysuria syndrome (FDS) with hypercalciuria (HCU), 19 children (15 girls and 4 boys; age range 15 months to 10 years) who presented with FDS alone (N=9) or with other associated clinical features (N=10; 6 with gross hematuria, 3 with microscopic hematuria and 1 with abdominal pain) were followed-up over 720 patient-months. Calcium loading test indicated absorptive HCU in 12 patients, renal HCU in 2, and in 5 the test was inconclusive. All patients were treated with a standard protocol after diagnosis. During follow-up, FDS recurred in 4 children, gross hematuria in 3, lumbar pain in 5, and 7 children developed urolithiasis within 3 to 60 months. The latter 7 children (4 with absorptive HCU and 1 with renal HCU) tended to be older than the other 12 (7.14 vs 5.08 years; p=0.11) and required a longer time to normalize urinary calcium excretion (16 vs 7 months; p<0.01). The initial urinary calcium excretion was similar between the patients with and those without stones (5.53 vs 5.6 mg/kg/d). In all other parameters measured, there were no statistically significant differences between the patients who initially presented with FDS alone and those with FDS accompanied with other urinary symptoms. We conclude that HCU and FDS in children can vary considerably in the clinical mode of presentation as well as its sequelae. Significant risk for urolithiasis burdens the children who require a longer time (>12 months) to normalize their hypercalciuria.

Key words: abdominal pain; calcium; calculi; hematuria; pediatrics; urolithiasis; urinary tract infections; urinary calculi

Idiopathic hypercalciuria is the most common metabolic abnormality associated with urolithiasis and non-glomerular hematuria in children (1-5). Diagnosed with increasing frequency, idiopathic hypercalciuria occurs in approximately 3-13% of the pediatric population (6-9). Several mechanisms may be involved in the pathogenesis of idiopathic hypercalciuria, but excessive gastro-intestinal absorption of dietary calcium appears to be the most frequent (10). Hematuria is the most common symptom associated with hypercalciuria (1,2,11,12) although the majority of children with hypercalciuria are asymptomatic. Other urinary symptoms such as dysuria, urinary frequency, lumbar pain, enuresis, and abdominal pain have also been noted (2,3,13-15), as well as the relationship between urolithiasis and gross hematuria associated with hypercalciuria (16). Frequency-dysuria syndrome in children generally results from bacterial infections but infection cannot be documented in many instances. Other causes, such as trauma, use of bubble baths, ingestion of lemon or apple juice, stress, lithiasis, and obstruction of the urinary tract are less likely (17). Idiopathic hypercalciuria has also been related to this urinary dysfunction and is often the first clinical indication of the disease (13). Long-term implications of untreated idiopathic hypercalciuria in children with frequency-dysuria syndrome are uncertain. Some investigators had encountered this association in small children and, despite having had difficulty controlling the symptoms, had not detected further clinical sequel (15), whereas Fivush et al (14) reported on two children who had dysuria on presentation, with one of them subsequently developing calculi. Since the relationship between idiopathic hyper-calciuria-associated frequency-dysuria syndrome and urolithiasis has not been well documented to date, the present study was designed to observe the natural history of untreated idiopathic hypercalciuria and frequency-dysuria syndrome by following-up, over a 720 patient-month period, 19 children with this condition.

Subjects and Methods
Between January 1993 and July 1998, all children with frequency-dysuria syndrome who were diagnosed to have idiopathic hypercalciuria were selected from the patients attending the Pediatric Clinic of the St. Joan de Reus Hospital, Spain. Hypercalciuria was defined as the urinary calcium excretion value >4mg/kg/day on at least two occasions during an unrestricted diet. No other cause of frequency-dysuria syndrome was identified in any of the cases.
Urinary pH and urine culture were routinely performed. Urinary excretion of calcium, creatinine, sodium, potassium, phosphate, uric acid, magnesium, oxalic acid, citrate, and urinary proteins were analyzed in 24-h urine samples. Blood samples were assayed for serum levels of parathyroid hormone, acid-base profile, creatinine, uric acid, urea, calcium, phosphate, sodium, potassium, alkaline phosphatase, and plasma proteins. Renal ultrasound was performed during the initial evaluation in all patients. During examination, particular attention was paid to family and personal history, physical appearance of external genitalia, and any clinical indications of hypercalciuria. During the follow-up, all children were examined every four months in the Pediatric Nephrology Outpatient Clinic; in addition to a complete physical examination, the examination included urine analysis and a non-fasting urinary calcium/creatinine ratio measurement. Serum electrolytes, creatinine, calcium, inorganic phosphate, 24h calcium excretion, and creatinine clearance were determined annually. Renal ultrasound examination was repeated every year as well. The standard treatment protocol consisted primarily of high fluid intake, salt restriction to <3g sodium/day, and recommended daily allowance for calcium of 600 mg/day. Hydrochlorothiazides (1-2mg/kg/d) were prescribed when the patient developed urolithiasis or when dietary modification was insufficient to normalize the hypercalciuria within six months. Absorptive idiopathic hypercalciuria was diagnosed if dietary modification was sufficient to normalize calcium. Oral calcium challenge was used to define idiopathic hypercalciuria subtypes in the patients who were unable to normalize their hypercalciuria with dietary calcium restriction alone. Renal hypercalciuria was defined as an increased fasting urinary calcium/creatinine ratio, and absorptive hypercalciuria was defined as a normal fasting ratio with an elevated urinary calcium/creatinine ratio following oral calcium load (18). All data were analyzed using the SPSS statistical package and the tests included Student's t test for paired and unpaired data, chi-square analysis, Mann-Whitney test, and multivariate analysis where appropriate. All values are presented as the mean±standard error of the mean (SEM) unless otherwise indicated and the level of statistical significance was set at p<0.05.

Results

Nineteen children with frequency-disuria syndrome and hypercalciuria fulfilled the criteria for the inclusion in the study (Table 1). Mean age at diagnosis was 5.84±2.71 years (range 15 months to 10 years). Fourteen of the children had a family history of urolithiasis. Ten patients presented with other associated clinical indicators, whereas the remainder had frequency disuria syndrome alone. Urinary tract infection had previously occurred in 6 children and 2 had a history of microhematuria. Physical examination findings, including blood pressure and the appearance of external genitalia, were normal in all children. Oxalate crystals were detected in 7 and pyuria in 3 cases during the follow-up period. Urine culture was sterile in all cases and serum concentrations of creatinine, calcium, phosphate, bicarbonate, uric acid, and parathyroid hormone were within the reference range for a pediatric population. One child presented with a high urinary oxalic acid excretion. Radiological and ultrasound renal examination of all the children showed no evidence of nephrocalcinosis.

Table 1: Clinical characteristics of 19 children with frequency-dysuria syndrome associated with hypercalciuria. View this table

Twelve children were classified as absorptive idiopathic hypercalciuria (2 by the calcium load test), 2 as renal idiopathic hypercalciuria, and the other 5 as indeterminate idiopathic hypercalciuria (inconclusive oral calcium challenge). The mean follow-up period for 19 children was 39.6±27.4 months (range 12 to 60 months). During the follow-up, 7 children developed urolithiasis, as detected by routine ultrasound. The interval between the diagnosis of idiopathic hypercalciuria-associated frequency-disuria syndrome and the development of urolithiasis was 23.6±25.2 months (range 3 to 60 months). One child had a relapse 2 years after the diagnosis of the first stone. Renal stones were located on the left side in 5 patients, and in 2 of them on the right side. Attempted passage of renal stones was successful in all cases, and no obstruction was detected.

Table 2: Comparison of clinical characteristics of the 7 children with frequency-dysuria syndrome (FDS) and hypercalciuria who developed urolithiasis with 12 children who did not develop urolithiasis (mean±SD). View this table
Children with urolithiasis took a longer time to normalize urinary calcium excretion compared to the group without stones (Table 2, p=0.01). Although the difference was not statistically significant, the group who developed stones tended to be older at the time of presentation with dysuria than those who did not develop stones (7.14±2.91 vs 5.08±2.39 years, respectively; p=0.11). No significant differences were observed with regard to the gender, type of hypercalciuria, urinary calcium excretion, or other frequency-dysuria syndrome-associated clinical features.

There was no difference in the clinical and laboratory characteristics of 9 patients who initially presented with frequency-dysuria syndrome alone and those who had frequency-dysuria syndrome together with other associated clinical features.

Clinical follow-up data on the children, including the 7 patients before the development of urolithiasis, showed a marked variability of clinical sequels. Among the 9 patients who had presented with FDS alone, dysuria occurred in 2, gross hematuria appeared in 3, and abdominal pain in other 2 subjects. Among the 6 patients who initially presented with gross hematuria and frequency-dysuria syndrome, dysuria occurred in 2 and lumbar pain appeared in 3 subjects. Hematuria did not recur. The 3 children who initially presented with frequency-dysuria syndrome and microhematuria continued to be asymptomatic after the initial frequency-dysuria syndrome episode. Clinical complications did not occur in 6 patients following the initial symptomology, despite the continued presence of hypercalciuria for about a year in one of these subjects. Six children presented frequency-dysuria syndrome, gross hematuria, and abdominal pain at various times during the course of the study, and 3 of them eventually developed urolithiasis. Frequency-dysuria syndrome recurred in only 4 patients. Persistent hematuria was not recorded. Clinical symptoms usually paralleled the degree of hypercalciuria but this was not a universal finding. Some children presented with persistently elevated calciuria without associated clinical manifestation.

Discussion

In adults, the most common clinical presentation of frequency-dysuria syndrome is nephrolithiasis associated with attendant clinical complications. In the pediatric population, however, most patients with frequency-dysuria syndrome are asymptomatic and, if symptomatic, they differ from adults in their clinical presentation. Hematuria is the most common presentation (2) but other symptoms, such as dysuria, urinary frequency, pyuria, enuresis, failure to thrive, and abdominal pain, have also been described (12).

Our experience also confirms that non-infectious dysuria alone or in combination with other urinary tract symptoms, such as urinary frequency or enuresis, can be associated with hypercalciuria. As observed in the present series of patients, the cause-effect linkage between hypercalciuria and urinary tract symptoms is supported by good clinical outcome after achieving normalization of the hypercalciuria and by the reappearance of the symptoms with the recurrence of hypercalciuria. Marked variability of the clinical symptoms was observed in our patients during the follow-up period. Most children developed different HCU-associated symptoms during the follow-up. The recurrence of hypercalciuria was accompanied with dysuria, hematuria, or abdominal pain. Clinical and laboratory characteristics of the 9 patients initially presenting with frequency-dysuria syndrome were similar to those in the rest of the patients who had initially presented with frequency-dysuria syndrome in conjunction with other clinical features. The data suggest that idiopathic hypercalciuria in childhood is an entity independent of the different modes of clinical presentation. These findings indicate a common pathophysiologic mechanism for the different clinical pictures of idiopathic hypercalciuria in children. Although the precise mechanism is unknown at present, possible mechanisms might include traumatic injury of renal tubular cells or urinary tract uroendothelial damage from crystalluria (18). The cysto-urethral syndrome, therefore, would be another form of the disease in young children and its pathophysiologic progress could be similar since, as demonstrated in the present study, the incidence of urolithiasis in the children who presented with frequency-dysuria syndrome alone was similar to the incidence in the group of children presenting with hematuria as well. Hence, for children presenting with a clinical picture of dysuria of a non-infectious origin and those with hematuria of non-glomerular origin, the level of urinary calcium excretion should be investigated so as to implement adequate treatment follow-up.
Hypercalciuria is the most frequently identified metabolic abnormality associated with nephrolithiasis in children (5,20,21). In the previous study, we observed that 16 out of 23 children with urolithiasis had idiopathic frequency-dysuria syndrome (4). In the present study, we have found that 7 out of 19 children with idiopathic hypercalciuria and frequency-dysuria syndrome developed nephrolithiasis within a rather short follow-up period. Children at a greater risk for the development of urolithiasis tended to be older and required a longer time to achieve normocalciuria. Using a plot of these two variables (Fig. 1) a high-risk group for urolithiasis could be defined. For example, if more than one year was needed to achieve normocalciuria, this would correctly identify 5 of the 7 children who developed urolithiasis, whereas only 1 of 12 children would be incorrectly assigned to the high-risk group. If the age-at-onset parameter is also included (<9 years of age), all 7 patients developing urolithiasis would have been correctly predicted. Hematuria and abdominal pain, on the other hand, did not appear to increase the risk of nephrolithiasis in these patients. Cervera et al (2) reported an increased risk of developing stones only in the children with frequency-dysuria syndrome associated with urological malformations. García et al (16) found that 10 of 58 (17%) children with hematuria and frequency-dysuria syndrome developed renal calculi. The mean interval between diagnosis of hypercalciuria and urinary stones was 13.1 months. These children were older than those who did not develop lithiasis (16). These findings are very similar to our clinical data.

Children with symptomatic frequency-dysuria syndrome are at risk for future calculus formation. Reports indicate that 13-23% of children with frequency-dysuria syndrome-associated hematuria develop urolithiasis (5,13,16). In the present study, 7 out of 19 children with urinary tract symptoms associated with HCU developed stones. Most of these children improved clinically when urinary calcium excretion decreased even if it was not brought down to the normal range. This situation appears to be well-tolerated by the patients who are asymptomatic in spite of maintaining high calcium levels over a protracted period; the concomitant risk of urolithiasis is, however, considerably increased. We suggest that all children with symptomatic frequency-dysuria syndrome ought to be encouraged to follow general preventative measures, such as increasing fluid intake together with a reduction of dietary sodium and calcium. If these measures do not achieve normalization of the calciuria within 6 to 8 months in spite of the alleviation of clinical symptoms, thiazide therapy ought to be implemented so as to decrease the risk of lithiasis. Since lithiasis develops within approximately 2 years of the clinical debut of the hypercalciuria, this period is critical for bringing hypercalciuria under control.

In confirmation of the study by García et al (16), the classification of the children with hypercalciuria into different sub-types based on the calcium loading test was of little clinical use with respect to therapeutic conduct since, it was not a per se factor influencing the subsequent development of lithiasis.

We conclude that urinary tract symptoms of non-infectious origin are often associated with hypercalciuria in children and that its clinical presentation, as with hematuria, carries an increased risk of urolithiasis. Our observation indicate that hypercalciuria in childhood may have different clinical modes in different individuals and at different time points in the same individual as well. To diminish the risk of lithiasis, methods to normalize the hypercalciuria should be pursued, irrespective of the current clinical picture, so as to ensure that elevated values do not persist longer that 12 months.

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