0022-5347/94/1524-1226$03.00/0
THE JOURNAL OF UROLOGY
Vol. 152, 1226–1228, October 1994
Printed in U.S.A.

URINARY INCONTINENCE DUE TO IDIOPATHIC HYPERCALCIURIA IN CHILDREN

PRAYONG VACHVANICHSANONG, MARICARMEN MALAGON AND EDDIE S. MOORE*

From the Department of Pediatrics, University of Tennessee Graduate School of Medicine, Knoxville, Tennessee

ABSTRACT

Idiopathic hypercalciuria is known to cause many nonstone urinary tract disorders in childhood. In addition to being the most common cause of microhematuria in children, our study demonstrates that idiopathic hypercalciuria is also frequently associated with urinary incontinence of all types. Of 124 children evaluated for idiopathic hypercalciuria 28 (23%) had urinary incontinence. Of the 28 children 15 (54%) had nocturnal, 6 (21%) diurnal, and 7 (25%) nocturnal and diurnal incontinence. The random urinary calcium-creatinine ratio, which was used to screen for hypercalciuria, should be part of the initial evaluation for urinary incontinence in children. Diagnosis may be confirmed by quantitative urinary calcium excretion. Most urinary incontinence in children that is due to idiopathic hypercalciuria responds to a combination of general treatment for hypercalciuria or thiazide diuretics.

KEY WORDS: calcium metabolism disorders, enuresis, urinary incontinence, bladder

Idiopathic hypercalciuria, a hereditary disorder occurring in children and adults, is the most common cause of metabolic urolithiasis in all age groups.[1, 2] In 1981 we first reported that nonstone clinical manifestations of idiopathic hypercalciuria were more common in children than urolithiasis.[3] These disorders include microscopic and gross hematuria, abdominal colic, lumbar pain, the urinary frequency/urgency syndrome, pyuria and dysuria. Recently, we noted that urinary incontinence was the fourth most common problem in children referred for evaluation of idiopathic hypercalciuria. Since pediatric and general urologists are often the first consultants to evaluate children with urinary tract disorders, they must develop an increased awareness of idiopathic hypercalciuria as a possible cause of urinary incontinence. We report our experience with 28 children who had urinary incontinence due to idiopathic hypercalciuria.

PATIENTS AND METHODS

We evaluated 124 children referred to our center from April 1988 to April 1993 who were diagnosed with idiopathic hypercalciuria based on a quantitative urinary calcium excretion of more than 2 mg./kg. daily or a nonfasting random urinary calcium-creatinine concentration ratio of more than 0.17 mg./mg.[4] Hypercalciuria was defined as idiopathic when secondary causes could not be found.[5] Urinary incontinence was defined as the leakage of urine at least once weekly in children age 5 years and older[6] and as the leakage of urine after 3 consecutive months or more of dryness in children age 5 years and younger. Nocturnal urinary incontinence refers to night wetting only, daytime incontinence to wetting only during the day and mixed urinary incontinence to day and night wetting.

Once the diagnosis of idiopathic hypercalciuria was established patients were started on general treatment measures alone or in combination with specific pharmacotherapy. General treatment consisted of liberal fluid intake to decrease urinary calcium saturation, decreased dietary oxalate to reduce urinary calcium crystallization as the oxalate and, since urinary calcium excretion is linearly correlated with sodium excretion, decreased dietary salt intake. Specific pharmacotherapy consisted of thiazide diuretics and, when necessary, analgesics and antispasmodics. The response to treatment for urinary incontinence due to idiopathic hypercalciuria was defined as no response, improved if there was at least a 50% decrease in the number of days or nights per week incontinent or complete resolution. Statistical analysis of mean values was by the Student t test. A p value of ≤ 0.05 was considered significant.

Accepted for publication January 21, 1994.
* Requests for reprints: Department of Pediatrics, University of Tennessee Graduate School of Medicine, Box U-113, 1924 Alcoa Highway, Knoxville, Tennessee 37920.

RESULTS

The 11 boys and 17 girls with urinary incontinence due to idiopathic hypercalciuria represented 23% of all 124 children with symptomatic idiopathic hypercalciuria. Mean age was 7.3 ± 3.2 years (range 3.2 to 10.1) for boys and 6.7 ± 3.0 years (range 3.3 to 14.8) for girls, which was not significantly different. In addition, the mean age of the children with urinary incontinence was not different from those with idiopathic hypercalciuria and urinary continence (6.9 ± 2.6 versus 6.5 ± 3.9 years). Of the 28 children with incontinence 7 (25%) were younger than 5 years, and they had been continent for more than 3 months before the onset of urinary incontinence.

Table 1 shows correlation of clinical diagnosis with age, sex and urinary calcium excretion. Of the children 15 (54%) had nocturnal incontinence (9 boys and 6 girls), 6 (21%) had diurnal incontinence (1 boy and 5 girls) and 7 (25%) had mixed incontinence (1 boy and 6 girls). As shown in table 1 mean random urinary calcium-creatinine concentration ratio was 0.27 ± 0.11 mg./mg. for all children with urinary incontinence, which was not different than the mean for those with idiopathic hypercalciuria without urinary incontinence (0.34 ± 0.29 mg./mg.). Mean random urinary calcium-creatinine concentration ratio for boys with incontinence was not different than the mean for girls with incontinence due to idiopathic hypercalciuria (0.25 ± 0.11 versus 0.28 ± 0.11 mg./mg.). Only 4 of the 28 children (14%) had random urinary calcium-creatinine concentration ratios less than 0.17 mg./mg. but they all had abnormal quantitative urinary calcium excretion. Quantitative urinary calcium excretion in 20 children ranged from 1.37 to 16.00 mg./kg. body weight daily (mean 4.46 ± 3.01). Mean daily calcium excretion in boys was 3.74 ± 1.08 mg./kg. compared to 5.12 ± 3.56 mg./kg. in girls, which was not significantly different. Three of 20 children (15%) had urinary calcium excretion of less than 2 mg./kg. daily but they had an abnormal random urinary calcium-creatinine concentration ratio.

TABLE 1. *Age, gender, type of incontinence and urinary calcium excretion of 28 children with urinary incontinence and idiopathic hypercalciuria.*

	Total	Boys	Girls
No. pts. (%)	28	11 (39.3)	17 (60.7)
Pt. age (yrs.):			
Mean	6.9 ± 2.6	7.3 ± 3.2	6.7 ± 3.0
Range	3.2–14.8	3.2–10.1	3.3–14.8
No. incontinent:			
Nocturnal	15	9	6
Diurnal	6	1	5
Day and night	7	1	6
Urinary calcium-creatinine concentration ratio (mg./mg.):			
Mean	0.27 ± 0.11	0.25 ± 0.11	0.28 ± 0.11
Range	0.09–0.58	0.09–0.43	0.12–0.58
Urinary calcium excretion (mg./kg. daily):			
Mean	4.46 ± 3.01 (20 pts.)	3.74 ± 1.08 (7 pts.)	5.12 ± 3.56 (13 pts.)
Range	1.37–16	1.82–5.1	1.37–16

Table 2 shows the associated clinical and laboratory manifestations in the children with incontinence due to idiopathic hypercalciuria. Six children (21%) had associated microscopic hematuria (3 to 5 or more red blood cells per high power field) and 1 gross hematuria. Significant bacteriuria (10^5 or more) was present in 13 children (46%) at evaluation. All children received appropriate antibiotic therapy to sterilize the urine before idiopathic hypercalciuria was considered to be the cause of incontinence. Additional associated symptoms included bladder spasm in 46%, abdominal pain in 32%, dysuria in 21% and lumbar pain in 4%. No child with incontinence showed evidence of stones. However, family history was positive for urolithiasis in 13 cases (46%), including 6 in which maternal and paternal family histories were positive.

Uroradiographic studies were done in 23 cases (82%), including renal ultrasound in 21 (91%), excretory urography in 2 (9%), voiding cystourethrography in 9 (39%) and nuclear renal scan in 1 (4%). Cystoscopy was normal in 1 child with incontinence before referral to us and in 1 consulted by telephone before the diagnosis of idiopathic hypercalciuria. Renal ultrasound revealed a cyst in the kidney in 1 child and a possible renal stone that was not visualized on excretory urography in 1. All other uroradiological studies were normal. Metabolic studies were normal including serum urea nitrogen and creatinine, acid-base status, serum calcium, phosphorus and alkaline phosphatase. Serum activity for 1,25(OH)2 vitamin D_3 was elevated in 3 of 17 children (18%) and immunoreactive parathyroid hormone was elevated in 1 of 11 children (9%).

Treatment for idiopathic hypercalciuria resulted in complete resolution of incontinence in 9 children (32%), a greater than 50% decrease in incontinence in 10 (36%) who were considered improved and no response in 1 (4%) (table 3). In 8 children (28%) response to treatment could not be determined because of failure to return for further evaluation.

TABLE 3. *Response to treatment of urinary incontinence due to idiopathic hypercalciuria*

Type of Incontinence	Total No. Pts.	No. Response (%)			
		Complete	Improved	None	Unknown
Nighttime	15	5 (33)	4 (27)	0	6 (40)
Daytime	6	1 (17)	3 (50)	1 (17)	1 (17)
Day and night	7	3 (43)	3 (43)	0	1 (14)

DISCUSSION

The development of urinary continence involves complex physiological mechanisms and there is disagreement as to the age when it is complete.[7] Failure to gain voluntary control of urination or loss of prior control is termed incontinence or enuresis. Types of urinary incontinence differ in the amount of urine loss (partial or total) and in the pattern of loss (daytime, nighttime or day and night).[7] Nighttime wetting is reported to be the most common pattern of urine loss. In our study nocturnal incontinence due to idiopathic hypercalciuria was more common, and diurnal and combined day and night urinary loss was equal. Nocturnal incontinence due to idiopathic hypercalciuria was more common in boys, whereas diurnal and mixed day and night incontinence was more common in girls. Most children with nocturnal incontinence due to idiopathic hypercalciuria had apparent total bladder emptying, whereas those with diurnal incontinence tended to have partial urine loss.

There are many theories regarding the causes of incontinence, including developmental, habit-deficiency, environmental, genetic, psychogenic and organic,[8] but none currently includes idiopathic hypercalciuria as defined by our study. The incidence of organic lesions or a pathological condition causing incontinence is low and the extent of evaluation that is required is disputed. In general, obtaining a comprehensive history, including family history of enuresis or urolithiasis, and performance of a thorough physical examination with neurological assessment are emphasized. Almost half of our 28 children with incontinence due to idiopathic hypercalciuria had a positive family history for renal stone disease. Initial laboratory studies usually consist of urinalysis and urine culture in children with urinary incontinence. Significant bacteriuria was found in 13 children, all of whom received antibiotic treatment with no significant effect on incontinence. Although idiopathic hypercalciuria is thought to be the cause of incontinence, we recommend voiding cystourethrography in children with idiopathic hypercalciuria and associated significant bacteriuria. Furthermore, if there is recurrent urinary tract infection, consideration should be given to the use of isotope scans to rule out renal parenchymal scarring.

The associated hematuria was similar to that described in previous reports, and idiopathic hypercalciuria is now believed to be the most common cause of microscopic hematuria in childhood.[9] In addition, abdominal pain, lumbar pain and

TABLE 2. *Additional clinical manifestations associated with urinary incontinence due to idiopathic hypercalciuria*

	No. Pts. (%)
Bladder spasm	13 (46.4)
Recurrent urinary tract infection	13 (46.4)
Abdominal pain	9 (32.1)
Dysuria	6 (21.4)
Microscopic hematuria	6 (21.4)
Gross hematuria	1 (3.6)
Lumbar pain	1 (3.6)
Stones	0 (0)

dysuria have also been shown to be associated with idiopathic hypercalciuria in childhood.[3] Unfortunately, some children with incontinence undergo unnecessary invasive procedures, such as cystoscopy. Our study indicates that idiopathic hypercalciuria should be considered as a possible etiology of urinary incontinence during the initial evaluation and before invasive studies are performed.

Normal urinary calcium excretion in childhood is controversial with hypercalciuria defined as ranging from greater than 2 to 8 mg./kg. daily.[4, 10] Since hypercalciuria in adults is generally defined as greater than 2 mg./kg. daily and children must maintain a positive calcium balance for growth, we recommend that hypercalciuria in children be defined as greater than 2 mg./kg. daily when quantitative urinary calcium excretion can be determined.[11] All of our children with incontinence due to idiopathic hypercalciuria had hypercalciuria as demonstrated by a random urinary calcium-creatinine concentration ratio or by quantitative excretion. However, since fasting influences the urinary calcium-creatinine concentration ratio the first morning urine is not a reliable specimen for this determination and these results in our study represent late morning or afternoon urine specimens. Mean quantitative urinary calcium excretion in children with incontinence due to idiopathic hypercalciuria was within the range defined as abnormal in most reports.[4, 10] Although there were more girls than boys, calcium excretion was not different. Specific idiopathic hypercalciuria subtypes were not completely investigated but 3 children had elevated serum vitamin D and 1 had apparent secondary hyperparathyroidism. At least 3 idiopathic hypercalciuria subtypes have been reported in children, that is hyperabsorptive, renal leak and sodium-dependent.[12–14] Except for a possible response to subtype specific treatment, it does not appear that the subtype of idiopathic hypercalciuria has a role in causing incontinence.

How can hypercalciuria cause incontinence? We previously speculated that calcium crystals cause irritation to urinary tract epithelium, producing noncalculous clinical manifestations.[3] Therefore, it is our hypothesis that calcium crystals in these children irritate the bladder, causing it to contract or the bladder outlet to relax, which results in involuntary voiding. Although bladder filling is the usual stimulus to void, filling would not be necessary with this mechanism. The associated findings of hematuria and bacteriuria support a role for crystal injury since these conditions are common in overt stone disease.[12]

The long-term prognosis for children with urinary incontinence due to idiopathic hypercalciuria is uncertain. We, as well as others, have noted a good response to treatment of symptomatic idiopathic hypercalciuria in childhood.[12, 15] However, the experience to date is that up to 72% of children with hematuria due to idiopathic hypercalciuria will ultimately have stones from a few months to 15 years later.[12, 16, 17] Therefore, not only is it important to diagnose idiopathic hypercalciuria as a cause of urinary incontinence to avoid unnecessary procedures, such as cystoscopy, but also to identify those children who may be at risk for future stone disease.

Since demonstration of incontinence with idiopathic hypercalciuria during childhood is a new observation, some skepticism is expected. However, the convincing aspect of our report is the overwhelmingly positive response of urinary incontinence to treatment for hypercalciuria. Although incontinence in children has a high incidence of spontaneous resolution, the cause and effect relationship of treatment in our cases appears to be real. It is intriguing to postulate that underlying idiopathic hypercalciuria may be responsible, at least in part, for the failure of some children with incontinence to respond to other forms of treatment, such as hormone replacement, behavior modification and bladder stretching. It is conceivable that some children with incontinence due to idiopathic hypercalciuria who do not have total resolution with thiazides may have an additional benefit from combined therapy with these current treatment modalities. Therefore, the large number of children studied and the documentation of hypercalciuria with positive treatment response indicate that, until further experience suggests otherwise, the simple procedure of a random urinary calcium-creatinine concentration ratio should be part of the routine evaluation for incontinence. Furthermore, if the random ratio is normal but there is a strong family history of urolithiasis or incontinence is unexplained, quantitative urine calcium determination may help establish the diagnosis of idiopathic hypercalciuria.

REFERENCES

1. Stapleton, F. B., McKay, C. P. and Noe, H. N.: Urolithiasis in children: the role of hypercalciuria. Ped. Ann., **16:** 980, 1987.
2. Pak, C. Y., Britton, F., Peterson, R., Ward, D., Northcutt, C., Breslau, N. A., McGuire, J., Sakhaee, K., Bush, S., Nicar, M., Norman, D. A. and Peters, P.: Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. Amer. J. Med., **69:** 19, 1980.
3. Moore, E. S.: Hypercalciuria in children. Contr. Nephrol., **27:** 20, 1981.
4. Moore, E. S., Coe, F. L., McMann, B. J. and Favus, M. J.: Idiopathic hypercalciuria in children: prevalence and metabolic characteristics. J. Ped., **92:** 906, 1978.
5. Henneman, P. H., Benedict, P. H., Forbes, A. P. and Dudley, H. R.: Idiopathic hypercalciuria. New Engl. J. Med., **259:** 802, 1958.
6. Iester, A., Marchesi, A., Cohen, A., Iester, M., Bagnasco, F. and Bonelli, R.: Functional enuresis: pharmacological versus behavioral treatment. Child. Nerv. Syst., **7:** 106, 1991.
7. Himsl, K. K. and Hurwitz, R. S.: Pediatric urinary incontinence. Urol. Clin. N. Amer., **18:** 283, 1991.
8. Järvelin, M. R., Moilanen, I., Kangas, P., Moring, K., Vikeväinen-Tervonen, L., Huttunen, N. P. and Seppänen, J.: Aetiological and precipitating factors for childhood enuresis. Acta Paed. Scand., **80:** 361, 1991.
9. Perrone, H. C., Ajzen, H., Toporovski, J. and Schor, N.: Metabolic disturbance as a cause of recurrent hematuria in children. Kidney Int., **39:** 707, 1991.
10. Royer, P., Habib, R., Mathieu, H., Broyer, M. and Walsh, A.: Idiopathic hypercalciuria. In: Major Problems in Clinical Pediatrics. Edited by A. J. Schaffer. Philadelphia: W. B. Saunders Co., pp. 65–95, 1974.
11. Coe, F. L. and Bushinsky, D. A.: Pathophysiology of hypercalciuria. Amer. J. Physiol., part 2, **247:** F1, 1984.
12. Cervera, A., Corral, M. J., Gómez Campdera, F. J., De Lecea, A. M., Luque, A. and Lópes Gómez, J. M.: Idiopathic hypercalciuria in children. Classification, clinical manifestations and outcome. Acta Paed. Scand., **76:** 271, 1987.
13. Pak, C. Y., Kaplan, R., Bone, H., Townsend, J. and Waters, O.: A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. New Engl. J. Med., **292:** 497, 1975.
14. Hymes, L. C. and Warshaw, B. L.: Idiopathic hypercalciuria. Renal and absorptive subtypes in children. Amer. J. Dis. Child., **138:** 176, 1984.
15. Stapleton, F. B.: Idiopathic hypercalciuria in children. Sem. Nephrol., **3:** 116, 1983.
16. Roy, S., III, Stapleton, F. B., Noe, H. N. and Jerkins, G.: Hematuria preceding renal calculus formation in children with hypercalciuria. J. Ped., **99:** 712, 1981.
17. Túri, S., Visy, M., Vissy, A., Jászai, V., Czirbesz, Z., Haszon, I., Szelid, Z. and Ferkis, I.: Long-term follow-up of patients with persistent/recurrent, isolated haematuria: a Hungarian multicentre study. Ped. Nephrol., **3:** 235, 1989.