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Metabolic disturbance as a cause of recurrent hematuria in children

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Metabolic disturbance as a cause of recurrent hematuria in children. To evaluate metabolic disturbance as a cause of hematuria, 250 children, aged eight months to fourteen years, with recurrent hematuria were studied. In the present series, metabolic disturbance was mainly due to idiopathic hypercalciuria (IH), the most common etiology of hematuria without proteinuria in childhood. Sixty-seven (27%) of the children had IH, ten children (4%) had hyperuricosuria, and 27 (11%) had nephrolithiasis. To better characterize the IH into renal (RH) or absorptive hypercalciuria (AH) subtypes, 45 of the 67 children (ranging age from six to twelve years) were further submitted to an oral calcium load test. Eighteen patients (40%) had AH, 7 (15.5%) RH and 20 (44.4%) could not be classified as having AH or RH [indeterminant (ID) idiopathic hypercalciuria group]. Intravenous pyelography or ultrasound were normal in all children. The oral calcium load test may be useful in characterizing the subtype of IH in some children; however, a great number of the IH children were characterized as indeterminant. Also hyperuricosuria, recently described as another metabolic disturbance associated with hematuria, may be an important cause of recurrent hematuria in children.

Idiopathic hypercalciuria (IH), a disorder characterized by an increase of calcium urinary excretion higher than 4 mg/kg/day, is a frequent metabolic disorder in childhood and has been associated with clinical findings such as urolithiasis [1], hematuria [2], and juvenile rheumatoid arthritis [3]. Recently, an association between asymptomatic hematuria and hypercalciuria prior to clinical or roentgenographic evidence of urolithiasis has been emphasized [2, 4, 5]. In 1981, Moore [5] reported that hematuria without urolithiasis was the initial clinical manifestation in eight of twenty-three children with IH. Recently, hyperuricosuria has also been associated with hematuria [6].

However, evaluation of urinary calcium and uric acid excretion has not been routinely carried out in children with macroscopic or intermittent hematuria, and the prevalence of IH as well as hyperuricosuria (HU) in a population of children with hematuria remains unknown in most pediatric centers. In view of the reported familial incidence of IH [3, 7, 8], it was also interesting to find that in 86% of children studied with gross hematuria and a family history of urolithiasis, hypercalciuria was present [2]. On the basis of the pathogenic mechanisms two major subtypes of IH, renal and absorptive hypercalciuria, can be distinguished utilizing an oral calcium load test [9]. The characterization of these groups of IH have been reported to be of clinical value in formulating a rational therapeutic regimen for children with IH associated with hematuria and/or urolithiasis [10]. This paper therefore, was undertaken to analyze metabolic disturbances associated with hematuria and to assess the clinical value of the oral calcium load test in characterizing IH subtypes in children. Furthermore, we examined the clinical evolution of children with IH, who were submitted to different therapeutic approaches based upon classification by the oral calcium test.

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Methods

During the last five years (1984 to 1989), 250 children with recurrent hematuria (more than 5 red blood cells per high powered field), aged 8 months to 14 years old were evaluated in our nephrology department. Twenty-seven percent of those children had only hypercalciuria as a cause of the hematuria without proteinuria. The presenting symptom was microscopic in 18% and gross hematuria in 82%. Among them, we studied the first 45 of a total of 67 children with IH with oral calcium load test. Ten healthy children, aged 5 to 9 years, without history of renal disease were used as controls. After an Ethical Committee approval and a consent obtained from parents of the patients and control group, each child was submitted to an oral calcium load test similar to that described for Pak et al which was adapted to children by Stapleton et al [9, 11]. On their habitual diets, the patients fasted from 8 p.m. of the preceding evening to 8 a.m. the next morning, except for 200 ml of distilled water at 8 p.m., 10 p.m. and 6 a.m. Urine was collected for two hours and, after a light breakfast, an oral calcium load (1 g/1.73 m^2 of body surface area) was administered. An equilibration period of 30 minutes was followed and a new collection of urine was obtained over the next 210 minutes. Blood samples were collected just before calcium administration. Serum calcium, uric acid and phosphorus were measured, a creatinine clearance was calculated and urinary cyclic AMP (cAMP) determined. Three 24-hour urinary collections, with a 7 to 10 day interval, were analyzed for uric acid, creatinine and calcium excretion in each child. Three 24-hour samples of urine were collected as there was a variability in the daily UCa excretion, and the highest value was chosen for the IH diagnosis because of its relationship with a high risk of nucleation. Cyclic AMP was measured by the method of Broadus [12], calcium by atomic absorption technique (290-B Perkin Elmer,

Atomic Spectrophotometer model; Perkin-Elmer, Norwalk, Connecticut, USA); uric acid by Follin and Denis' technique [13]; phosphorus by Fishe and Subbarrow method [14] and creatinine by Jaffé technique [15]. All patients were submitted to intravenous pyelogram and/or ultrasound examinations. Patients with RH were submitted to a prospective treatment with hydrochlorothiazide (0.5 mg/kg/day), and those with AH were treated with rice bran or calcium restricted diet (400 to 500 mg of calcium/day) for three to twelve months. Children with HU were treated with allopurinol and/or purine restricted diet for 1 to 3 months. For indeterminant IH potassium citrate was administered (0.5 mEq/kg/day). Urinary excretion of calcium, uric acid, urinalysis and urine culture were performed monthly. The patients have been followed in our outpatient clinic.

Laboratory criteria

The diagnosis of IH was established by an urinary calcium excretion > 4 mg/kg/day in one or more of the three 24-hour urinary collections, with normal serum calcium concentration while ingesting an habitual diet [16]. The data provided by Stapleton et al [3] is similar to that observed in previous research with 140 Brazilian children: mean urinary calcium excretion was 1.6 ± 0.1 mg/kg/day ($\overline{X}$ ± SE) in children aged 2 to 7 years; 1.9 ± 0.1 mg/kg/day in children aged 7 to 12 years and 1.2 ± 0.2 mg/kg/day in children aged 12 to 18 years. Hence 4 mg/kg/day ($\overline{X}$ ± 2 SD) was considered to be the upper limit for 24-hour urinary calcium excretion. Renal hypercalciuria (RH) was defined as a fasting U_{Ca}/U_{Cr} concentration ratio greater than 0.21 [9]. Absorptive hypercalciuria (AH) was defined as a fasting U_{Ca}/U_{Cr} concentration rate less than 0.21 and a urinary Ca/Cr index greater than 0.27 after calcium administration [10]. Finally, a third group of children with IH was characterized by 24-hour urinary calcium excretion greater than 4 mg/kg/day, but the oral calcium load test was not able to define if the children had an AH or RH subtype. Those children had U_{Ca}/U_{Cr} fasting ratio less than 0.21 and loading less than 0.27. Therefore they were characterized as the indeterminant (ID) IH group.

Uric acid hyperexcretion is considered to be excessive if greater than $\overline{X}$ ± 2 SD for age per 24 hours [17], similar to the results in normal children in São Paulo [16]: 615 mg/day ($\overline{X}$ ± 2 SD) in children aged 2 to 7 years; 580 mg/day in children aged 7 to 12 years and 628 mg/day in children aged 12 to 18 years.

Statistical analysis were performed by Student's unpaired *t*-test and the Fisher test for the L/F ratio (Table 2). Results are expressed as mean ± standard error ($\overline{X}$ ± SE).

Results

Metabolic disturbances were the common etiologies of recurrent hematuria in childhood (Table 1), IH occurred in 27%, uric acid hyperexcretion was present in 4%, and 11% had nephrolithiasis. In the IH group 11 of 45 (24.4%) children presented with uric acid hyperexcretion. The first group of forty-five children with hematuria and hypercalciuria were submitted to the oral calcium load test. There were 20 female and 25 male subjects, evenly distributed throughout all age groups, with an age range of 6 to 12 years old (mean 8.8 ± 0.4 years). The control group of 10 children (6 boys and 4 girls) ranged in ages from 5 to 9 years (mean 8.4 ± 0.9 years), which was similar to the age range of IH children. Children with HU (6 female and 4 male) had a mean age of 8.6 years.

Table 1. Recurrent hematuria in children: Etiology

	Number	Percent	Mean age *years*
Hypercalciuria	67	27	8.7 ± 0.5[a]
Uric acid hyperexcretion	10	4	8.6 ± 1.0
Nephrolithiasis	27	11	9.1 ± 0.2
Glomerulopathies			
Berger	15	6	10.5 ± 0.8
Alport	19	7	7.7 ± 0.6
Others	45	18	9.8 ± 0.9
Urinary tract infection	14	6	7.5 ± 1.1
Renal malformation	8	3	6.3 ± 0.5
After renal trauma	2	1	11.0 ± 0.7
Without diagnosis	43	17	9.3 ± 1.7
Total	250	100	

[a] $\overline{X}$ ± SE

The incidence of urolithiasis in the control group was null. However, the IH group had positive family history in 16 of 45 children (35.5%); the RH group had positive family history in 4 of 7 children (57%), the AH group had positive family history in 9 of 18 (50%), the ID group had positive family history in 8 of 20 children (40%), and the HU group had positive family history in 5 of 10 children (50%).

No statistical differences were observed in serum concentrations of calcium, uric acid or phosphorus serum concentrations among the five groups. Also, no alterations in glomerular filtration rate, as estimated by creatinine clearance, were found. The higher 24-hour urinary calcium excretion in children in the renal, absorptive and ID groups was significant, especially when compared with the control group ($P < 0.0005$; Table 2). The mean urinary calcium was 1.6 ± 0.3 mg/kg/day in the control group, 6.8 ± 1.0 mg/kg/day in children with RH, 6.6 ± 0.6 mg/kg/day in the AH group and 6.0 ± 0.3 mg/kg/day in the ID. Urinary cyclic AMP excretion was normal in all children (Table 2).

According to their responses, children were classified as having renal hypercalciuria, absorptive hypercalciuria or indeterminant IH (ID). Before calcium administration, no significant differences in the urinary Ca/Cr concentration ratio were observed among the control group (0.12 ± 0.02, AH (0.07 ± 0.01), or ID groups (0.09 ± 0.01), as shown in Table 2. However, children with RH showed a significant difference with this ratio, 0.22 ± 0.01 ($P < 0.0005$) when compared with the control group.

After the calcium load, urinary Ca/Cr concentration ratios for both RH (0.30 ± 0.01) and AH (0.27 ± 0.03) groups were significantly greater than those observed in the control group (0.15 ± 0.02), $P < 0.0005$ and $P < 0.0025$, respectively. The increase in U_{Ca}/U_{Cr} concentration ratio on children with AH, when compared with the fasting ratio, was almost four times greater. This increment was not found in the control group or in patients with RH or ID.

Urinary uric acid excretion was elevated in 10 children (Table 3). Calcium excretion was normal in each child. The intravenous pyelogram and/or ultrasonography examinations were normal in all evaluated children (100%).

After the treatment with hydrochlorothiazide, calcium restriction diet (or rice bran), potassium citrate, allopurinol or purine restricted diet, urinary calcium or uric acid concentra-

Table 2. Urinary values for calcium and cAMP

	Ratio (U_{Ca}/U_{Cr})			Urinary values	
	Fasting (F)	Load (L)	L/F	Ca *mg/kg/24 hr*	cAMP *nmol/dl GFR*
Control (N = 10)	0.12 ± 0.02[a]	0.15 ± 0.02	1.25	1.6 ± 0.3	2.7 ± 1.5
Children with					
IH (N = 45)	0.12 ± 0.01	0.26 ± 0.03[b]	2.15	6.7 ± 0.5[b]	1.9 ± 0.6
RH (N = 7)	0.22 ± 0.01[b]	0.30 ± 0.01[b]	1.36	6.8 ± 1.0[b]	2.5 ± 0.3
AH (N = 18)	0.07 ± 0.01	0.27 ± 0.03[b]	3.86[b]	6.6 ± 0.6[b]	1.5 ± 0.2
ID (N = 20)	0.09 ± 0.01	0.15 ± 0.01	1.66	6.0 ± 0.3[b]	1.9 ± 0.2

Abbreviations are: cAMP, Cyclic adenosine monophosphate; IH, idiopathic hypercalciuria; RH, renal hypercalciuria; AH, absorptive hypercalciuria; ID, indeterminant; GFR, glomerular filtration rate; (L/F), increment of the ratio U_{Ca}/U_{Cr} from fasting to load of calcium intake.
[a] $\bar{X}$ ± SE
[b] $P < 0.05$ vs. control

Table 3. Uric acid hyperexcretion in childhood

Patient	Sex	Age *years*	U_{Ca} *mg/kg*	UUrAc *mg/day*	UUrAc mg/1.73 m² BSA
1	F	8	2.7	1100	1655
2	M	9	2.0	650	938
3	M	8	2.2	690	1356
4	F	3	2.6	810	2335
5	F	9	1.0	800	1281
6	M	3	3.0	518	1318
7	F	12	0.9	936	1157
8	F	13	1.0	1100	1410
9	M	11	3.0	650	903
10	F	10	1.0	2700	5190

Abbreviations are: F, female; M, male; UUrAc, urinary uric acid.

Table 4. IH and hematuria: Evolution during 6 to 12 months

	Treatment	U_{Ca} *mg/kg/day* before	U_{Ca} *mg/kg/day* after	Renal stone formation
RH				
Treated (N = 3)	HCT	6.8	2.7	0/3
Not treated (N = 1)	—	7.2	5.2	1/1
Irregular treatment (N = 3)	HCT/—	5.7	4.2	2/3
AH				
Treated (N = 8)	diet or rice bran	6.5	3.0	0/8
Not treated (N = 6)	—	5.2	4.1	2/6
Irregular treatment (N = 4)	diet/— rice bran	7.1	3.7	2/4
ID				
Treated (N = 5)	potassium citrate	6.4	5.1	0/5
Not treated (N = 10)	—	5.2	3.9	2/10
Irregular treatment (N = 5)	potassium citrate/—	6.1	4.0	0/5

Abbreviations are: RH, renal hypercalciuria; AH, absorptive hypercalciuria; IH, indeterminant hypercalciuria; HCT, hydrochlorothiazide.

tions returned to normal in each patient. The decreased urinary calcium excretion was accompanied by disappearance of hematuria in four patients with HU. None of the treated patients developed renal stone formation, while the 5 of 17 patients not treated developed stones and 4 of 12 irregular treated patients developed nephrolithiasis (Table 4). Irregular treatment is characterized as spontaneous interruption of treatment after one or two months, followed by sporadic treatment at irregular intervals.

Discussion

Increased urinary calcium excretion (IH) is an important metabolic event since it accounts for 38 to 70% of calculi disease [1, 18], 26 to 36% of childhood hematuria [19] and it is observed in 3 to 7% of normal children [10, 16]. There are many reports suggesting IH as a main cause of recurrent hematuria in children [19], but only a few reports describe hyperuricosuria as a possible cause of recurrent hematuria in children [6] and adults [20]. Bayle and Mancheno [6] recently reported five cases of children with hematuria due to hyperuricosuria and have verified the disappearance of the hematuria when uricosuria was reduced. Among the 250 children in the present study who had hematuria, a striking 31% of the cases were due to metabolic disturbances. IH may result from at least two pathogenetical mechanisms, namely an excessive intestinal absorption of calcium (AH) or an inadequate tubular reabsorption of calcium from the glomerular filtrate (RH) [9]. However, it is not clearly established whether AH and RH are two pathological entities or if they represent different manifestations of the same disease [21]. It is also possible that both subtypes are related to a same complex of proximal renal tubular defect [1]. However, distinguishing these two subtypes is thought to be of considerable clinical importance, since each of them may require a different therapeutic approach [21–23]. In AH, treatment is directed toward decreasing intestinal calcium absorption with neutral phosphate or rice bran supplements [22] and/or with a low calcium diet [23]. On the other hand, a thiazide diuretic and/or amiloride is effective in reducing calcium excretion in RH during long-term therapy [21]. In AH, urinary calcium excretion is only transiently reduced after a period of thiazide administration [18]. Thiazide therapy was prescribed for children with RH until urinary calcium return to normal (3 to 12 months). The benefit of this treatment and the long-term risk of hydrochlorothiazide administration are unclear [1, 21]. During the last two years we have had the opportunity of treating and following children with IH in order to verify if the treatment had any clinical benefit. As previously described by Roy et al [4], five children with recurrent hematuria were discovered to have IH only after a passage of calcium oxalate stone. All five

children had been evaluated months to years previously for unexplained hematuria without evidence of urinary calculi at the time of initial evaluation [4]. Similarly, in the present series of 45 children with IH and hematuria, radiological studies with either intravenous pyelogram or ultrasound (or both) were normal in all children. No specific cause for the increase in urinary calcium or uric acid excretion were determined, and hence it was compatible with the diagnosis of IH and HU. Uric acid levels in plasma being the same in normal children and those children with hyperuricosuria suggest that an overproduction of urate could be responsible for this process. Long-term observation showed a high incidence of urolithiasis in these children with hematuria and IH. Within two years, 11 of 45 (24%) of the IH group and 2 of 10 (20%) of the HU group developed renal stones after variable periods of recurrent hematuria (unpublished data).

The present study suggests that routine measurement of urinary calcium and uric acid excretion is warranted in children with unexplained hematuria, and that an oral calcium load test appears to distinguish RH from AH in some children found to have hypercalciuria. In this series 7 of 45 (15%) and 18 of 45 (40%) presented RH and AH subtypes of IH, respectively. Moreover, our data also suggest that IH and HU are more likely to be the cause of hematuria in children in whom there is a family history of urolithiasis [7, 8]. In such children, a continued surveillance for warning signs of calculi is very important, as reported by Stapleton [19] in a prospective multicenter study that described IH in 76 (35%) patients among 215 children with hematuria, and 74% of the IH group had at least one relative with urolithiasis [19].

In conclusion, these data indicate that metabolic disturbance is the most common definable cause of hematuria in our population of children. Therefore, it is very important to consider hypercalciuria and uric acid hyperexcretion during the investigation of hematuria. IH and hyperuricosuria have their origins in childhood; early diagnosis and appropriate treatment may reduce the incidence of renal stones in children as well as in adults.

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