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RENAL FUNCTION IN CHILDREN WITH HYPERCALCIURIA*

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Hypercalciuria is a common problem causing symptoms such as abdominal pain, hematuria and enuresis, and leading to stone formation. It results from a renal tubular calcium "leak" or intestinal hyper-reabsorption of calcium. This study was performed to determine whether renal functional impairment was present in children with hypercalciuria. The study group comprised 298 children who were screened for hypercalciuria by means of urinary calcium/creatinine (UCa/UCr) ratio. The renal functions of 18 children (6.4%) detected as having hypercalciuria with Ca/Cr ratios of greater than 0.18 in their spot urines were evaluated. Results were compared with those of the healthy control group. The rate of hypercalciuria did not vary significantly between the boys and girls ($p > 0.05$). The mean value of daily calcium excretion was 6.42 + 3.93 mg/kg/day in the children with hypercalciuria, which was significantly different from that of the control group ($p < 0.01$). When the values of creatinine, osmolar and free water clearances, fractional excretion of sodium and tubular reabsorption of phosphorus were compared between the patient and control groups, the difference was not significant ($p > 0.05$). Urinary N-acetyl-β-D-glucosaminidase (NAG) excretion, which was described as the creatinine ratio, was significantly higher in the children with hypercalciuria. These findings suggest that in the presence of normal renal functional studies in children with hypercalciuria, tubular injury can be detected by NAG, which is a more sensitive marker of renal tubular injury. *Key words: hypercalciuria, renal function, N-acetyl-β-D-glucosaminidase.*

Hypercalciuria is more common in children than adults and causes symptoms such as hematuria, dysuria, enuresis, colic and growth failure and leads to urolithiasis[1,2]. The incidence of asymptomatic idiopathic hypercalciuria has been reported as 2.2-6.4 percent among children[3,4]. Idiopathic hypercalciuria was found in 30 percent of patients who peresented with hematuria and five to seven percent of patients who had urolithiasis[3-5]. Hypercalciuria can be due to impaired renal reabsorption of calcium or excessive gastrointestinal absorption of dietary calcium. In childhood, renal tubular reabsorption of calcium is more likely to be impaired, as reported previously[6]. Previous studies in adult patients with renal hypercalciuria have described various defects in either proximal or distal renal tubular function. In most previous pediatric studies, renal and absorptive hypercalciuria were not distinguished; thus, renal tubular defects associated with a tubular abnormality in renal hypercalciuria may not have been apparent. In

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this study we evaluated renal function in a group of 18 children with idiopathic hypercalciuria. The proximal tubulus was also evaluated by means of N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme which is present in high concentrations in renal tubular cells[7]. The results were compared with those of the control group.

Material and Methods

The study group comprised 298 children (220 boys and 78 girls) between four and 17 years in an orphanage. All children were screened for hypercalciuria, and those whose urinary calcium/creatinine ratios (U_{Ca}/U_{Cr}) were below 0.18 in their spot urines were excluded. A 24-hour urine specimen was collected for the determination of daily calcium excretion in the goup whose urine was examined twice and U_{Ca}/U_{Cr} values were found to be greater than 0.18. Eighteen children with urine calcium values greater than 4 mg/kg/day were included in the study, while 21 healthy children (13 girls and 8 boys) were taken as the control group. All the children were questioned regarding the presence of abdominal pain, dysuria, hematuria, enuresis and increased frequency of urination as well as any drug use. Physical examinations were done and the patients' weights, heights and blood pressures were recorded. Blood calcium (Ca), phosphorus (P), alkaline phosphatase, blood urea nitrogen (BUN), creatinine (Cr), sodium (Na), potassium (K) and osmolarities were determined in both groups. A 24-hour urine specimen was collected for Na, Ca, Cr, P and NAG. Clearances of Cr (C_{Cr}), fractional excretion of sodium (FE_{Na}), tubular reabsorption of phosphorus (TRP), and clearances of potassium (C_K), osmolarity (C_{osm}), and free water (C_{H2O}) were calculated. Urinary NAG activity was determined spectrophotometrically[8]. The enzyme activity in each urine sample was expressed as the NAG U/mmol creatinine. NAG excretion was determined as U_{NAG}/U_{Cr} mmol. U_{Ca}/U_{Cr} urinary sodium/creatinine ratios (U_{Na}/U_{Cr}) were determined from fasting urines. Urinalysis was performed in all of the children for density, pH, proteinuria and microscopic examination. Urine cultures were taken. Direct roentgenogram of the abdomen was evaluated for calculi and bone density.

Statistical analyses were performed using Student's t test. The values are reported as mean ± SE.

Results

Twelve boys (5.5%) and six girls (7.7%) comprised the study group, which consisted of those 18 children (6.0%) who were detected as having hypercalciuria with U_{Ca}/U_{Cr} values of greater than 0.18 in two fasting urines, and daily Ca excretion of greater than 4 mg/kg. The rate of hypercalciuria was similar among boys and girls ($p > 0.05$, Table I). Eight children (44.4%) had abdominal and/

or groin pain, while two children (11.1%) had enuresis nocturna, and four children (2 boys, 2 girls) had hematuria. No pathogenic microorganism was detected in their urine cultures. Biochemical analyses of blood for BUN, Cr, Na, K, Ca, P and alkaline phosphatase were within normal limits, and when compared with the control group the difference was not statistically significant ($p > 0.05$). The mean value of U_{Ca}/U_{Cr} was 0.34 ± 0.20 in the fasting urines and 0.25 ± 0.06 mg/mg in the patients' second urines; when compared with the U_{Ca}/U_{Cr} values of the control group (0.12 ± 0.04 mg/mg) the difference was statistically significant ($p < 0.01$, Table II). Ca excretion in the 24-hour collected urine in the study group (6.42 ± 3.93 mg/kg/day) was higher than in the control group (1.92 ± 0.78), and the difference was significant ($p < 0.001$). Clearances of creatinine, osmolar and free water as well as values of FE_{Na} and TRP were normal, and there was no significant difference between the two groups. The U_{Na}/U_{Cr} ratio was not different between the two groups ($p > 0.05$). U_{NAG}/U_{Cr} values were higher in the study group (242.86 ± 82.74) than the control group (133.15 ± 98.69), and the difference was statistically significant ($p < 0.001$, Table II). Roentgenograms of the abdomen and bone densities were normal.

Table I: The Rate of Hypercalciuria Among Girls and Boys

Sex	Hyercalciuria (+)	%	Hyercalciuria (-)	%	Total
Female	6	7.69	72	92.31	78
Male	12	5.45	208	94.55	220

Table II: Renal Function of the Patients and the Control Group

Renal Function	Patients	Control	p
U_{Ca}/U_{Cr}	0.25 ± 0.06	0.12 ± 0.04	< 0.01
U_{Ca}/U_{Na}	0.21 ± 0.39	0.04 ± 0.02	< 0.001
U_{Na}/U_{Cr}	2.49 ± 1.83	2.72 ± 1.66	> 0.05
C_{Cr}	87.39 ± 8.01	98.05 ± 12.75	> 0.05
FE_{Na}	1.39 ± 1.08	1.16 ± 0.62	> 0.05
TRP	92.53 ± 2.54	95.47 ± 2.75	> 0.05
C_{osm}	2.37 ± 1.23	3.16 ± 1.01	> 0.05
C_{H20}	-1.67 ± 1.01	-1.87 ± 1.10	> 0.05
U_{NAG}/U_{Cr}	242.8 ± 82.74	133.15 ± 98.69	< 0.001

Discussion

The long morbidity associated with hypercalciuria is due to the development of renal stones[9]. This requires clinicians both to attempt to prevent it and to identify those children already affected at presentation. The incidence of

hypercalciuria varies between 2.2 and 6.0 percent in different countries[3, 4]. Turkey ranks among the countries with a high incidence of urolithiasis. The incidence was found to be 4.2 percent in a study done in Ankara[10]. In our study the rate of hypercalciuria was 6.0 percent among 298 children, with 7.7 percent of girls and 5.5 percent of boys affected. In the literature there are studies demonstrating the incidence of hypercalciuria to be higher in males[5, 11], while in other series no difference was found between the two sexes[9]. In some studies an autosomal dominant inheritance of hypercalciuria has been demonstrated[12, 13]. Because our study was performed in an orphanage, we could not interpret the inheritance, but there are two siblings among our patients.

Renal tubular reabsorption of calcium is more likely to be impaired in childhood[11, 14]. Because the U_{Ca}/U_{Cr} values of the fasting urines of 18 children were greater than 0.18, the absorptive type of hypercalciuria was eliminated. In our study serum levels of calcium, phosphorus and alkaline phosphatase were within normal limits, and there was no statistically significant difference between the study and control groups; moreover, radiological evaluation of bone mineralization was normal. For that reason renal hypercalciuria was considered to be more likely.

Renal tubular transport of calcium is an energy-requiring process and Ca-Mg-ATP-ase dependent. More than 50 percent of reabsorption takes place in the proximal tubulus, parathyroid hormone while (PTH) increases Ca reabsorption in the distal segments of the tubulus[6]. Recently proximal and distal tubulus damage due to prolonged crytalluria has been reported in adults[15]. On the other hand, Stapleton et al.[6] evaluated the renal functions of 10 children with hypercalciuria and detected impairment in the concentration ability of the kidney. In our study, the values of C_{Cr}, FE_{Na}, TRP, C_{osm} and C_{H20} were normal and statistically similar to the control group values. Because the children with hypercalciuria were selected as the study group, U_{Ca}/U_{Cr} values were higher than among controls. In a previous study, dysfunctional proximal renal tubular sodium transport was suggested in idiopathic hypercalciuria (IH), but dietary sodium was not controlled in that study[16]. Stapleton and Miller[6] restricted sodium in their study group with IH and pointed out that daily sodium excretion closely approximated dietary sodium intake. In our study, values of FE_{Na} and U_{Na}/U_{Cr} were not different from those of the control group.

NAG is a lysosomal enzyme with a molecular weight that precludes its filtration at the glomerulus, and urinary NAG excretion has been found to be a sensitive marker of renal tubular injury[17]. It has been reported that increased excretion of calcium causes renal damage by way of microcalculi focuses and leads to renal tubular injury. For that reason we studied urinary NAG excretion in both the study and control groups. U_{NAG}/U_{Cr} values of the children with hypercalciuria were much

higher than in the control group ($p < 0.001$), as was reported in previous studies[16, 17]. In conclusion, in our study tubular dysfunction was confirmed by means of NAG, which was grossly abnormal in the group with hypercalciuria.

REFERENCES

1. Stapleton FB, Noe HN, Roy S, 3d, Jerkins G. Hypercalciuria in children with urolithiasis. Am J Dis Child 1982; 136: 675-678.
2. Roy S, 3d, Stapleton FB, Noe HN, Jerkins G. Hematuria preceding renal calculus formation in children with hypercalciuria. J Pediatr 1981; 99: 712-715.
3. Moore ES, Coe FI, McMann G, Favus MJ. Idiopathic hypercalciuria in children: prevalence and metabolic characteristics. J Pediatr 1978; 92: 906-910.
4. Coe FL, Canterburry JM, Firpo JJ. Evidence for hyperparathyroidism in idiopathic hypercalciuria. J Clin Invest 1973; 52: 134-142.
5. Stapleton FB, Roy S 3d, Noe HN, Jerkins G. Hypercalciuria in children with hematuria. N Engl J Med 1984; 310: 1345-1348.
6. Stapleton FB, Miller LA. Renal function in children with idiopathic hypercalciuria. Pediatr Nephrol 1988; 2: 229-235.
7. Kunin CM, Chesney RW, Craig WA, England AC, De Angelis C. Enzymuria as a marker of renal injury and disease: studies on N-acetyl-β-D-glucosaminidase in the general population and in patients with renal disease. Pediatrics 1978; 62: 751-760.
8. Horak E, Hopfer MS, Sundermann WF. Spectrophotometric assay for urinary N-acetyl-β-D-glucosamiindase activity. Clin Chem 1983; 29: 1717-1719.
9. Effect of hydrochlorothiazide on renal hypercalciuria. Child Nephrol Urol 1992; 12: 6-9.
10. Buyan N, Saatçi Ü, Bakkaloğlu A, Beşbaş N. Okul çocuklarında asemptomatik hiperkalsiüri: epidemiyoloji ve patogenez. Çocuk Sağlığı ve Hastalıkları Dergisi 1989; 32: 43-50.
11. Langman CB, Moore ES. Hypercalciuria in clinical pediatrics. A review. Clin Pediatr (Phila) 1984; 23: 135-137.
12. Coe FL, Parks JH, Moore ES. Familial idiopathic hypercalciuria. N Engl J Med 1979; 300: 337-340.
13. Buyan N, Saatçi Ü, Bakkaloğlu A, Beşbaş N. Familial idiopathic hypercalciuria. Turk J Pediatr 1988; 30: 145-151.
14. Carvera A, Corral FJ, Gomez C. Idiopathic hypercalciuria in children: classification, clinical manifestations and outcome. Acta Paediatr Scand 1987; 76: 271-278.
15. Lemann J Jr, Adams ND, Oray RW. Urinary calcium excretion in human beings. New Engl J Med 1979; 301: 535-541.
16. Aladjem M, Modan M, Lusky A, et al. Idiopathic hypercalciuria: a familial generalized renal hyperexcretory state. Kidney Int 1983; 24: 549-554.
17. Stapleton FB, Chesney RW, Behrmann AT, Miller LS. Increased urinary excretion of renal N-acetyl beta glucosaminidase in hypercalciuria. Am J Dis Child 1985; 139: 950-95.