PATTERN OF INHERITANCE OF IDIOPATHIC HYPERCALCIURIA IN TWO FAMILIES

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Abstract- Idiopathic hypercalciuria is a leading cause of frequency-dysuria syndrome in childhood. Different modes of inheritance have been suggested in this disease. This article presents the occurrence of idiopathic hypercalciuria in all children of two families. In the first family, a 5.5 year old girl with a history of renal stones and dysuria due to hypercalciuria, had two involved brothers and one sister. In the second family, hypercalciuria and medullary nephrocalcinosis were detected in two siblings who were admitted for polyuria and dysuria. Idiopathic type of hypercalciuria was diagnosed in these two families by normal laboratory exams and exclusion of other causes of normocalcemic hypercalciuria. According to the involvement of all offsprings (both sexes) in these two families, it is suggested that idiopathic hypercalciuria is an autosomal dominant disease with complete penetration.

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Key words: Idiopathic hypercalciuria, inheritance, childhood, autosomal dominant

INTRODUCTION

Idiopathic hypercalciuria is a common metabolic abnormality in children, which could present with abdominal pain, dysuria, nephrolithiasis, hematuria and osteoporosis (1). It is a type of familial hypercalciuria without any definite genetic defect and characterized by normal serum calcium, (2, 3) normal PTH level (rarely increased or decreased) (4, 5), increased urinary excretion of cAMP and hydroxyproline (6) and normal to increased level of 1, 25 $(OH)_2$ D_3 (2, 3). It is the major cause of renal stones with normal serum calcium in adulthood (4). The incidence in children ranges from 2-4% (7, 8) to 7-10% (2).

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The mode of inheritance is controversial in different references. In this study, a discussion is presented about the inheritance of this disease.

CASE REPORT

Two families were studied for hypercalciuria as follows:

First family: A 5.5 years old girl was admitted for dysuria and poor weight gain. She had a history of renal stones and urinary tract infection (without any definite follow up). Family history was negative for renal disease. Parents were relatives and healthy. Her weight was 13.5 kg, and height about 4 years of age. In laboratory exams complete blood count (CBC), blood chemistry, arterial blood gas (ABGs) and parathyroid hormone (PTH) level were normal. In urinalysis, she had pyuria, hematuria with isomorphic RBCs, without any RBC cast and proteinuria. Urine culture was negative. Bone age

was about 2.5 years. Microcalcifications of 2 mm diameter with bilateral fullness of renal pelvises were detected in ultrasonography. Voiding cystourethrography was normal. Severe hypercalciuria revealed in 24 hours urine sampling (Table1). Treatment was started by a regimen of low salt diet, hydrochlorothiazide and potassium citrate.

The patient's family members were studied for hematuria and hypercalciuria. Both her sister and two brothers had isolated microscopic hematuria with hypercalciuria. Serum PTH and blood chemistry were normal. Two of them had microcalcifications in renal ultrasound, which dissolved after appropriate treatment. Audiometry and ophthalmoscopic exams were negative.

Second family: A 10 year old girl was screened for polyuria and dysuria. She had a history of previous urinary tract infection (UTI). CBC, biochemical profiles, PTH and ABG were normal, and hypercalciuria detected in urine sampling (Table 2). She had medullary nephrocalcinosis in renal ultrasound. Her 5 year old brother was admitted in hospital for radial fracture and polyuria. He also had hypercalciuria, medullary nephrocalcinosis and significant osteoporosis in bone densitometry. Other reasons for polyuria were excluded in these two cases.

The two family parents had no cooperation for screening of hypercalciuria.

Idiopathic hypercalciuria was suggested in these two families by excluding other causes of normocalcemic hypercalciuria such as granulomatous disease, malignancy, renal tubular acidosis, Bartter syndrome, Dent's disease, hyperparathyroidism, Cushing disease, immobilization, Lasix abuse and vitamin D toxicity were excluded by history, physical exams and specific laboratory and radiologic exams (4, 5, 2).

Table 1. 24 hours urine sampling in the first family

Patients	Calcium (mg/kg)	Uric acid (mg/kg)	PTH (10-65) (pg/ml)
Index case	37	3	47
Sister	15	7	31
Brother1	9	10	29
Brother2	10		40

Table 2. 24 hours urine sampling in the second family

Patients	Calcium (mg/kg)	Oxalate (mg/kg)	Uric acid (mg/kg)	PTH (pg/ml)
Index case	15	1	9	40
Brother	14	1.5	10	25

DISCUSSION

Idiopathic hypercalciuria is a disease characterized by increased urinary calcium excretion on a regular diet with normal serum calcium level and without any associated disease (2). It is a complex disease resulting from an interaction between environmental and genetic factors (9). The mechanisms of idiopathic hypercalciuria consist of:

1: Increased intestinal calcium absorption due to high vitamin D receptor density with maximum velocity, primary increased production and sensitivity to $1,25(OH)_2$ D_3 or secondary increased production due to low calcium tubular reabsorption and finally increased function of 1αhydroxylase enzyme (2, 4, 5, 10-12). Increased urinary excretion and low plasma level of endothelin 1 has been reported in this group (13). 2: Increased calcium excretion due to a defect of renal reabsorption in thick ascending limb of Henle (2, 4, 5, 7, 14). Serum atrial natriuretic peptide (ANP) level is low in this type compared to the previous group (15). 3: Increased calcium bone resorption (2, 4), with high urinary hydroxyproline. Low bone density especially in cases with nephrocalcinosis and hyperuricosuria leads to bone fracture in this group (16-18). It is suggested that alteration in bone metabolism and osteoporosis already presents in 35% of patients at diagnosis and N- telopeptide is one of the most useful markers of bone alteration in this disease (19). Plasma rennin activity and serum aldosterone level are lower in absorptive than renal type, especially with nephrocalcinosis (15).

Biarchi and colleagues identified increased RBC calcium ATPase activity and a defect in distal renal tubule and intestinal Mg ATPase in these patients and their families (4). However, it was not the case in the study of Kocsis which showed no difference in Ca ATPase level and its activity in these patients (20).

Idiopathic hypercalciuria is a familial disease (3, 11) which occurs more in first degree relatives (3,

21) with suggested autosomal dominant inheritance (4, 12, 21, 22) with incomplete penetrance (2). 40% of adult patients have a positive family history (23). In a study by Hava, autosomal dominant inheritance suggested in renal type of idiopathic hypercalciuria, and not in absorptive type which means, this relates more to nutritional factors than genetics (24). But in two other researches, autosomal dominant inheritance suggested for absorptive type (12, 22). Of course, it is of importance to say that the current view is that, both disease mechanisms (absorptive and renal) occur in any patient with genetic hypercalciuria (2). On the other hand, other types of inheritance have been also reported. Goodman et al and some other references described polygenic inheritance in idiopathic hypercalciuria, relative to two codominant alleles, without describing any specific gene (3, 4, 25). Up to now, no specific chromosome or gene has been defined in this disorder. In experimental researches on rats, a genetic defect ($ch1_q$ 23.3- $_q24$) (26) and suggestive loci on chromosomes 4, 7, 10, 14 were detected. Responsible genes for encoding vitamin D receptors and calcium sensing receptor on chromosome 7 have been considered for idiopathic hypercalciuria in rats (11, 27). In a further study by Petrucci this relation was not found between hypercalciuria and calcium sensing receptor gene (28, 29).

In the present study, common involvement of all offsprings in these two families suggest autosomal dominant mode of inheritance with complete penetration in this disease and therefore it is recommended to screen all family members in any case with this problem to prevent complications such as renal stone.

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