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FAMILIAL IDIOPATHIC HYPERCALCIURIA*

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Recently, greater importance has been given to idiopathic hypercalciuria (IH) in children. It has been shown that 80-90 percent of all cases are asymptomatic. The prevalence of asymptomatic IH in children has been reported as 2.2-6.4 percent in some studies[1-4]. In one of our studies consisting of school-age children this incidence was recorded as 4.2 percent[5]. The pathogenesis of hypercalciuria is uncertain. Many pathogenetic mechanisms concerning renal tubular and intestinal defects in calcium absorption have been suggested. Some reports support the idea that IH could occur in more than one member in some families, and that the mode of inheritance strongly suggests the characteristics of autosomal dominant transmission[1,6].

IH is considered to be important in the genesis of urolithiasis which is an important pediatric problem in Turkey where this condition is endemic. In this study, we screened the first-degree relatives of IH patients to determine the occurrence of familial hypercalciuria among these patients and the frequency of hypercalciuria and urolithiasis in their families. It was emphasized that the families of the patients with IH and/or urolithiasis be screened to detect IH since most patients with IH are asymptomatic and should be followed up closely in order to prevent the occurrence of calcium stones.

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Material and Methods

Twelve families of 13 hypercalciuric children aged two to 13 years were studied. The subjects presented with abdominal pain, hematuria, dysuria, and irritability at the Pediatric Nephrology Unit of Hacettepe University Children's Hospital and were diagnosed as hypercalcuric. The diagnosis was made by demonstration of urine calcium/urine creatinine concentration ratios (U_{Ca}/U_{Cr}) on at least two second morning urine samples which were found to be greater than 0.21 mg/mg and quantitative urine calcium excretion greater than 4mg/kg body weight/day[7-9]. After the diagnosis was made, these 13 subjects had a further work-up of hypercalciuria to define whether it was idiopathic or secondary. Since no predisposing factor could be found, the children were diagnosed as having IH. Their parents agreed to participate in our family screening study. In this study, urine calcium excretions were determined in 37 first-degree relatives (parents and siblings) of 13 hypercalciuric children from 12 families (Cases 4 and 5 were siblings) as described above. Blood tests and x-ray screening could not be performed in the members found to be hypercalciuric.

Calcium in the urine was determined by the Ferro-Ham method[10] and the urine creatinine was determined by the Jaffe reaction[11]. The parents of our patients were then questioned about the occurrence of urinary tract stone disease in their first-degree and more distant relatives. The family members with urolithiasis were identified on the basis of this information. It has not been possible to contact these members in order to examine their urinary calcium excretion and abdominal x-rays.

Results

Our data showed that idiopathic hypercalciuria could occur in two inheritance patterns: familial and non-familial. In six families of our six idiopathic hypercalciuric patients all of the 18 first-degree relatives were found to be normocalciuric. This result suggested that IH occurred in a non-familial form in this group. Additionally, there was no history of urinary tract stone disease in the first-degree and more distant relatives of these six patients with non-familial IH.

On the other hand, among 19 first-degree relatives of seven hypercalciuric children (two of them siblings) from six other families, two of seven siblings and four of 12 parents were diagnosed as hypercalciuric. Both males and females were affected. This data showed that IH occurred in a familial form in the second group of our patients. The patients with familial IH accounted for 53.8 percent of the total patients with IH. The frequency of hypercalciuria in all 26 first-degree relatives including our seven patients with familial IH from six families was found to be 50 percent. It was learned that eight members of these six families had urinary tract stone disease. In addition to our two idiopathic hypercalciuric

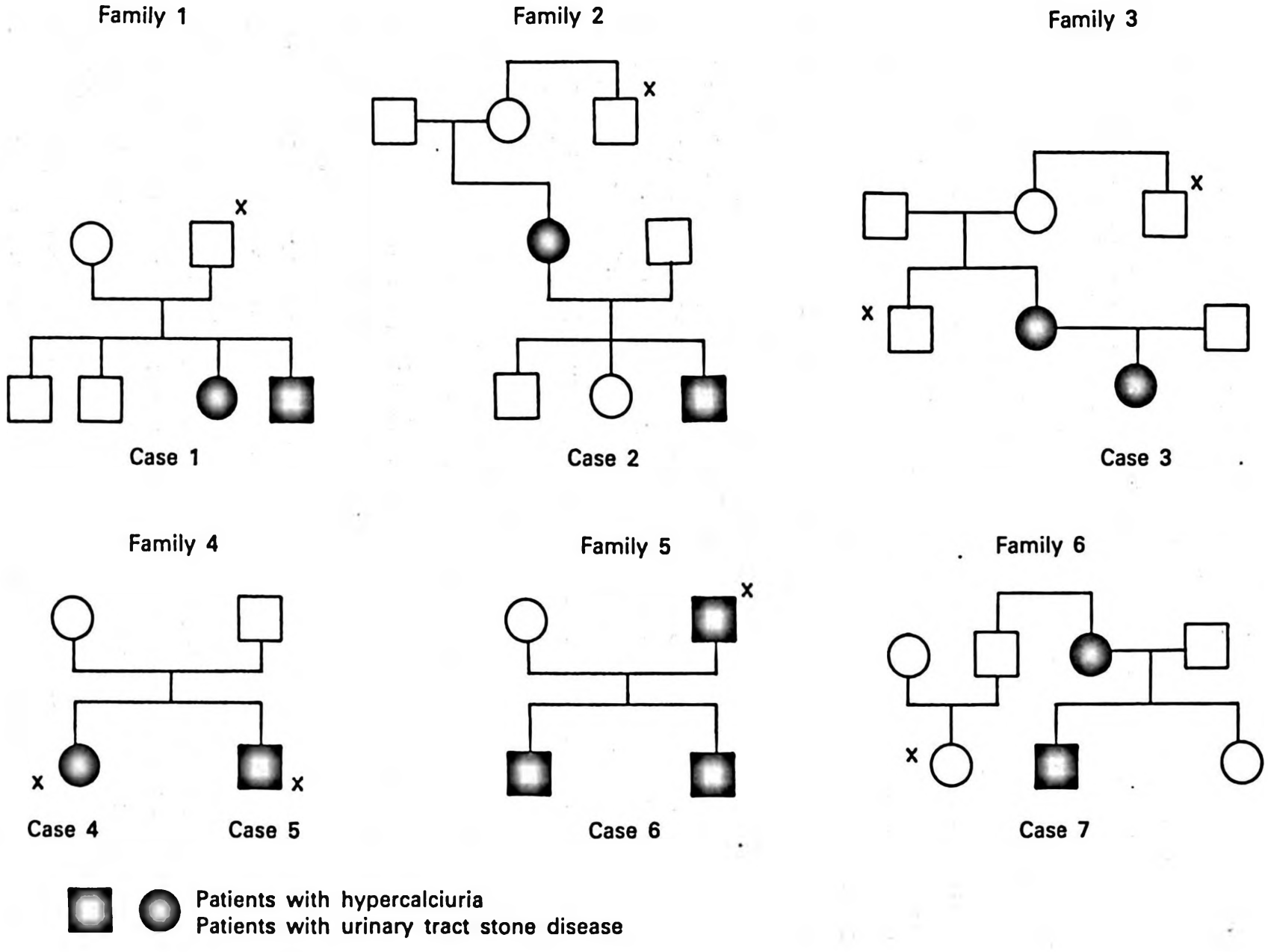

Fig. 1: Family pedigrees of seven patients who had hypercalciuric first-degree relatives.

TABLE I: Findings of Twelve Families of Thirteen Patients with Symptomatic Hypercalciuria

	Number of families screened	Number of family members screened	Number of familes with history of urolithiasis		Number of cases with hypercalciuria
			families	members	
Patients whose first-degree relatives had hypercalciuria	6	7* + 19	6	8	7* + 6
Patients whose first-degree relatives were normocalciuric	6	6* + 18	–	–	6*

* Patients with symptomatic hypercalciuria.

patients, who were siblings with urolithiasis (Case 4, 5), stone disease occurred in the fathers of two patients (Cases 1, 6; the father of Case 6 had hypercalciuria and chronic renal failure secondary to urinary tract stone disease) and in four more distant relatives of the other three patients (Cases 2, 3, 7). There was no female or male predominance in these eight members with urolithiasis. These findings are shown in Fig. 1 and Table I.

Discussion

The pathogenesis of IH remains uncertain although many mechanisms have been suggested[1,2]. There have been some reports that support the assumption that IH may occur in a familial form. Beilin and Clayton[12], who were the first to report the familial form of IH diagnosed this disease in a child, the child's brother and father. In another study, four male siblings in the same family were found to be hypercalciuric[13]. Lemann et al[14], reported that some of the relatives of eight patients, five of whom were hypercalciuric formed calcium stones. Buckalew et al[15], described a family in which 13 of 64 members had IH, six of these had nephrocalcinosis and four of these six had distal renal tubular acidosis. The largest family screening of the reports on IH was studied by Coe et al[6]. According to their findings, 73 relatives of nine patients had IH and recurrent calcium nephrolithiasis. Nineteen of the 44 first-degree relatives (43 percent) had IH, as compared to seven of 29 (29 percent) other relatives. Renal calculi, formed in 19 of the 44 first-degree relatives (43.1 percent) but in none of the others. They concluded that

the familial form of hypercalciuria appeared to be transmitted as an autosomal dominant trait. Furthermore, stone disease was frequent in first-degree relatives.

In this study, we showed that IH might occur as a familial or non-familial pattern of inheritance. Of 13 patients, six had non-familial IH. The remaining seven patients from six families had familial IH because 13 of 26 of their first-degree relatives were found to be hypercalciuric. There was no parental consanguinity in these six families. According to our data, the occurrence of familial IH among our 13 patients with IH was 53.8 percent and the occurrence of hypercalciuria in the first-degree relatives of the patients with familial IH was 50 percent. The second result was similar to the results of Coe et al[6]. Since both males and females and successive generations were affected and no parental consanguinity was present, an autosomal dominant pattern of inheritance may be considered in the cases with familial hypercalciuria although we could only study two successive generations of families.

When the parents of our 13 hypercalciuric patients were questioned about the occurrence of urinary tract stone disease in their relatives, no family history of urolithiasis of the six patients with non-familial IH from six families was detected, while eight members (including our two patients who were siblings) from the remaining six families of our seven patients with familial IH, had urinary tract stones.

IH is one of the most important causes of urinary tract stone disease. The incidence of IH in children with urolithiasis varies from 7 percent to 53 percent in various series of the literature[16]. In Turkey, urolithiasis is considered to be endemic[17]. In some studies, the family history has been reported to be positive in over 50 percent of the children in endemic areas[17]. Pediatric urolithiasis is one of the most common causes of chronic renal failure in Turkey and may result in many social and economic problems such as chronic renal failure requiring dialysis and transplantation.

In this study, it should be emphasized that there is a familial form of IH which is transmitted as an autosomal dominant trait and that urinary tract stones may be formed in first-degree or more distant relatives of patients with familial IH. Since 80-90 percent of IH cases are asymptomatic, family members of patients with IH and/or urinary tract stone disease should be screened not only to detect possible asymptomatic cases with the familial form of IH, but also to diagnose urinary tract stone disease which may have developed in relatives of patients with familial IH. The most common clinical signs and symptoms in children with IH are: microscopic hematuria, urinary frequency-urgency syndrome, daytime incontinence, colicky abdominal pain, recurrent urinary tract infections in female children and episodic gross hematuria[18].

Physicians must consider this entity and perform appropriate tests in order to establish the correct diagnosis. If preventive measures are taken such as the adjustment of fluid and salt oxalate intake, and thiazide therapy, calcium stone formation can be prevented. Since urolithiasis is endemic in our country, this subject is of great importance.

Summary

In this study, 37 first-degree relatives of 13 children with idiopathic hypercalciuria (IH) from 12 families are presented. We demonstrated that IH may occur in two patterns of inheritance: familial or non-familial. Since all of the 18 first-degree relatives of six patients with IH were normocalciuric, it was suggested that these patients had the non-familial form of IH. There was no history of urolithiasis in the relatives of these six patients. Of 26 members from the remaining six families, 13 including seven children with IH and six of their first-degree relatives had hypercalciuria. This data indicates that IH occurred in a familial form in this group. The occurrence of the familial form of IH among our 13 patients with IH was 53.8 percent and the frequency of hypercalciuria in the first-degree relatives of these patients with familial IH was 50 percent. Eight members including two children with IH and six first-degree and more distant relatives from the six families of seven patients with familial IH had urolithiasis. Our findings support the idea that the familial form of IH is transmitted as an autosomal dominant trait and urinary tract stones may be formed in relatives of patients with familial IH. It should be emphasized that the families of people with IH and/or urolithiasis be followed-up closely to prevent the occurrence of calcium stones since IH is known as an important cause of calcium stone formation and 80-90 percent of patients with IH are asymtomatic.

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