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ORIGINAL PAPER

Family history in stone disease: how important is it for the onset of the disease and the incidence of recurrence?

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Abstract The aim of this study was to evaluate the possible effect of a positive family history on the age at the onset of urinary stone disease and the frequency of subsequent symptomatic episodes relating to the disease. Between March 2006 and April 2009, patients with either a newly diagnosed or a previously documented stone disease were included in the study program. They were required to fill in a questionnaire and divided into two groups according to the positive family history of stone disease; group I comprised patients with a family history for urinary calculi and group II those without. Depending on the data obtained from questionnaires, all patients were evaluated in detail with respect to the age at the onset of the stone disease, stone passage and interventions over time, time to first recurrence (time interval between the onset of the disease and the first recurrence), number of total stone episodes and recurrence intervals. 1,595 patients suffering from urolithiasis with the mean age of 41.7 (14–69 years) were evaluated with respect to their past history of the disease. There were 437 patients in group I and 1,158 in group II. There was no statistically significant difference between the mean age value of two groups ($P = 0.09$). When both genders in group I were analyzed separately, female patients tended to have higher rate of family history positivity than males. Comparative evaluation of the age at the onset of the disease between the two groups did reveal that stone formation occured at younger ages in patients with positive family history [$P = 0.01$ (males), $P = 0.01$ (females)] and the mean age of onset of the disease was lower in males than females in group I ($P = 0.01$). Patients in group I had relatively more stone episodes from the onset of the disease [$P < 0.01$ (2–4 episodes), $P < 0.01$ ($\geq$5 episodes)]. Male patients were associated with higher number of stone episodes ($P = 0.01$). Mean time interval between recurrences was noted to be significantly shorter in group I patients when compared with patients in group II [$P < 0.01$ (males), $P = 0.02$ (females)]. In conclusion, our results showed that urinary stone formation may occur at younger ages and that the frequency of symptom episodes may be higher in patients with a positive family history. We believe that the positive family history for urinary stone disease could give us valuable information concerning the onset as well as the severity of the disease.

Keywords Urolithiasis · Onset age · Family history

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Introduction

With a constantly increasing incidence, urolithiasis has an estimated lifetime risk between 5 and 12% in Europe as well as in USA, affecting 13% of men and 7% of women populations [1, 2]. Because a considerable percent of patients will have a recurrence of renal colic within 5 years after the first stone episode, urolithiasis can be accepted as a chronic disease, with substantial economical consequences and great public health importance. The prevalence is increasing, on average 5%, ranging from 4 to 10% in different studies [3, 4]. Following the onset of the disease, the average recurrence rate is 31.5–50% within 5 years and more than 72% after 20 years [1, 4].

The high incidence along with the remarkable recurrence rates makes urolithiasis a serious social and economical problem for the societies. Although the symptoms and consequences are not life threatening in the majority of patients, stones in the urinary tract form a major cause of morbidity, hospitalization and days lost from work [2]. The number and the size of stones may increase in patients with recurrent stone disease making the treatment costs higher than the primary cases [5, 6]. Considering the increasing incidence and remarkable recurrence rates into account; epidemiological studies focusing on factors responsible for the formation of different stone types and also the natural course of the disease (i.e. recurrence rates) gained more importance than ever. Among these factors; although family history positivity has been subjected to a number of studies in recent years [7–10], the question of a familial predisposition towards stone formation and recurrence in urolithiasis has not been sufficiently examined.

The aim of this study was to evaluate the possible effect of a positive family history on the age at the onset of urinary stone disease and the frequency of subsequent symptomatic episodes relating to the disease.

Patients and methods

Between March 2006 and April 2009, patients with either a newly diagnosed or a previously documented stone disease were included into the study program. During the study program, all of the patients were evaluated with respect to their history of stones. They were required to fill in a questionnaire and divided into two groups according to the positive family history of stone disease; group I included patients with positive family history for urinary calculi and group II included patients without family history. The presence of previous stone disease, as well as the family history positivity has been confirmed from the documents available either from our own institution or from the other medical institutions where the previous diagnostic examinations were carried out. Depending on the data obtained from questionnaires, all patients were evaluated in detail with respect to the age at the onset of the stone disease, stone passage and interventions over time, time to first recurrence (time interval between the onset of the disease and the first recurrence), number of total stone episodes and recurrence intervals. In addition, the number and the type of family members of the patients in group I suffering from urolithiasis were noted. Stone episode was defined as the clinical and/or radiological finding recorded either at the diagnosis of a new stone formation or during the passage of an existing stone. Patients with one or more previous episodes of stone disease were defined as recurrent stone formers.

The data were analyzed using the SPSS 15.0 program. Parametric values were evaluated with *t* test and non-parametric descriptive values were tested with χ^2 or Fischer's exact test for statistical significance.

Study protocol has been approved by the ethics committee of the faculty and signed consent was obtained from all subjects before interview.

Results

1,595 patients suffering from urolithiasis with the mean age of 41.7 (14–69 years) were evaluated with respect to their past history of the disease. Male:female ratio was 1.38 (926:669).

Although group I consisted of 437 patients with a positive family history; group II consisted of 1,158 patients without any positive family history. There was no statistically significant difference between the mean age of two groups ($P = 0.09$) (Table 1). When both genders in group I were analyzed separately, female patients tended to have higher rate of family history positivity than males (F/M: 1.45) (Table 1). Table 1 summarizes the evaluation of the family members with documented urolithiasis.

Comparative evaluation of the age at the onset of the disease between the two groups did reveal that stone formation occurs at younger ages in patients with positive family history [$P = 0.01$ (males), $P = 0.01$ (females)] and the mean age of onset of the disease was lower in males than females in group I ($P = 0.01$) (Table 2). In addition to being affected by stone formation at younger ages; patients in group I had stone episodes relatively more often from the onset of the disease [$P < 0.01$ (2–4 episodes), $P < 0.01$ ($\geq$5 episodes)] where male patients were associated with higher number of stone episodes ($P = 0.01$) (Table 3). Although the majority of the patients in group II did have only one stone episode without any further recurrence; the percentage of patients having 2–5 recurrences as well as more than five recurrences were significantly higher in patients with positive family history (Table 3). Mean time interval between recurrences was noted to be significantly shorter in the same group of patients (25.4 ± 9.6 months in males and 27.3 ± 9.7 in females) when compared with patients in group II (34.6 ± 12.3 months in males and 33.9 ± 11.4 months in females) [$P < 0.01$ (males), $P = 0.02$ (females)] (Table 4).

Although patients in group I tended to have slightly higher percentage of multiple kidney stones, there was no statistically significant difference between the location, size and the number of stones in the two groups [$P = 0.21$ (kidney stones), $P = 0.14$ (ureteral stones), $P = 0.8$ (bladder stones)]. The chemical composition of the stones was available in 949 patients (59.4%). Although it was difficult to obtain the data from the evaluated files, most stones in the

Table 1 Evaluation of positive family history status with respect to the members affected

Total number of patients	1,595 (males 926, females 669)	M/F 1.38
Age range (mean)	14–69 (mean 41.7 years)	
Age at the onset of the stone disease	Males 31.7 ± 10.2 years Female 37.5 ± 12.8 years	Overall 34.0 ± 13.4 years
Presence of positive family history (n = 437, 27%)		
Male	178/437:40.7%	Age range (mean years): 3–58 (28.4)
Female	259/437:59.3%	Age range (mean years): 4–59 (31.2)
Evaluation of first-degree relatives in group I		
Mother or father	216 (49.4%)	M/F: 94/122
Mother and father	115 (26.3%)	M/F: 65/50
Mother, father and one sibling	61 (13.9%)	M/F: 25/36
Sibling (brother or sister)	45 (10.3%)	M/F: 24/21
Evaluation of second degree relatives in group I		
Aunt, uncle and cousin	157 (35.9%)	M/F: 88/69

	Positive family history	Negative family history
Comparison of two groups		
Number of patients	437	1,158
Number of male patients	178	748
Number of female patients	259	410
Age at the onset	34.0 ± 13.4 years	32.9 ± 10.9 years
Patients with the onset of the disease before the age of 15	67/437 (15.3%)	127/1,158 (10.9%)

Table 2 Evaluation of the mean age of patients in both the groups at first onset of the disease

	N	Males	Females
Mean age at the onset of the disease (years)			
Whole group	1,595	31.7 ± 10.2 (3–69)	37.5 ± 12.8 (5–64)
Positive family history	437	24.8 ± 9.4 (3–58)	28.3 ± 9.7 (4–59)
No family history	1,158	32.6 ± 11.9 (6–64)	33.8 ± 10.2 (7–66)

Table 3 Evaluation of stone episodes in both groups

Stone episodes	General (%)	Positive history (n = 437)	Negative history (n = 1,158)
1	921 (57.7)	202 (46.2%) M/F: 108/94 (1.14)	719 (62.1%)
2–4	439 (27.5)	149 (34.1%) M/F: 89/60 (1.48)	290 (25.1%)
5 and more	235 (14.7)	86 (19.7%) M/F: 51/35 (1.45)	149 (12.8%)

Table 4 Mean time interval period between the stone episodes in both the groups of patients

	N	Males	Females
Mean time interval between recurrences (months)			
Whole group	1,595	32.6 ± 10.4 (13–54)	30.8 ± 9.84 (15–62)
Positive family history	437	25.4 ± 9.66 (11–52)	27.3 ± 9.72 (12–46)
No family history	1,158	34.6 ± 12.3 (16–62)	33.9 ± 11.4 (17–58)

two groups were calcium stones (82% in group I and 84% in group II).

When we evaluated the previous history of stone removal procedures in both the groups, the number of interventions were relatively higher in group I. Majority of the patients in group II did not have previous stone removal procedures (P = 0.02) (Table 5).

A search for associated comorbidities (hypertension, diabetes, hypercholesterolemia, etc.) revealed a relatively higher coincidence of such pathologies in group I patients when compared with the patients in group II (30.4 and 18.9%, respectively).

Discussion

Increasing incidence and considerable recurrence rates along with severe renal functional consequences make urolithiasis a surgical and a medical problem which needs a

Table 5 Evaluation of previous surgery and the type of the procedures in both groups of patients

Previous intervention	General (n = 1,595) (%)	Positive history (n = 437) (%)	Negative history (n = 1,158) (%)
Pyelo/nephrolithotomy	42 (2.6)	29 (6.7)	27 (2.2)
Cystolithotomy	34 (2.1)	15 (3.6)	19 (1.5)
PCNL	168 (10.6)	94 (21.5)	118 (10.1)
Ureteroscopy	114 (7.1)	72 (16.4)	120 (10.3)
SWL	203 (12.7)	113 (25.9)	196 (16.8)
None	1,034 (64.8)	114 (25.9)	684 (59.1)

prompt diagnosis and appropriate management at all ages [11, 12]. Keeping these facts in mind, in addition to the successful surgical removal procedures; attempts have been made to limit the new stone formation after the first stone episode in stone formers.

In this regard; identification of recurrent stone formers is a crucial step for a proper treatment planning and also important as a solution for future problems induced by the disease [13]. Different studies reported recurrence rates of patients with urolithiasis as high as 30–50% 5 years after the first episode [14, 15] and calcium oxalate stones are most likely to re-form where recurrence rates have been reported to be 40% at 3 years, 74% at 10 years and 98% at 25 years [16–18]. Related with this subject, Strohmaier et al. [19] reviewed the literature well and reported 30–40% recurrence rates where the highest recurrence probability was during the first 4 years. Thus, associated morbidities and increasing socioeconomic costs of urolithiasis made it important to identify the patients at risk for close follow-up and early proper management planning [6, 12, 17, 20–22].

Management of this problem is increasingly relying on inhibiting stone growth and preventing formation of new stones; such a prophylactic approach requires identification of factors which predispose patients to urinary stone formation and several epidemiological factors on this aspect have been evaluated. Among the factors evaluated so far; studies focused on age, gender, ethnicity, past medical history, educational and social level along with the profession, dietary status and inherent genetic predisposition [1, 6, 23].

A variety of publications have focused on the possible effect of positive family history for the onset and recurrence as well as for the prevalence of urinary stones. However, the exact relationship between the familial predisposition and the stone formation in primary urolithiasis has been incompletely analyzed. Positive family history has been reported to be present in 17–37% of patients with stone disease when compared with 4–22% of normal healthy control subjects [7, 10]. In a well-designed epidemiological study, about 25% of patients with urinary stones have been found to be associated with a positive family history [8]. In another study, it was demonstrated that stone-forming patients with positive family history were affected by the disease at younger ages [9]. In a survey carried out in 380 patients in an outpatients' stone clinic, a majority of the patients with a documented family history, had experienced frequent recurrences when compared with the others. While in 55.4% of patients at least one first-degree relative suffered from renal stones; positive family history was more common in females (64.7%) than males (51.0%) and in those who had multiple recurrences [7]. In an evaluation of 214 calcium stone patients and 428 age and sex-matched controls; the authors observed a higher frequency of stone episodes among the first-degree relatives of stone patients compared with the relatives of controls. A family history of renal stones was more common among female (45%) and male patients (31%). Finally, the parents and siblings of renal stone patients with positive family history were found to have more calculi than the corresponding relatives of their spouses [24].

In the present study, we aimed to evaluate the possible effect of positive family history on recurrent stone formation and compare the data with stone-forming patients without any positive family history. The overall incidence of positive family history in stone-forming patients was 27%. Female gender seemed to have higher incidence of positive family history than males. Male gender tended to be afflicted by the disease at younger ages than females, which was more pronounced for the cases revealing a positive family history. This finding is important because the involvement of one or more members of the family with stone disease may be a good predictor for the onset of the disease at younger ages in next generations. Another important parameter was the number of stone recurrences and the interval between these episodes. Evaluation of the patients with positive family history did clearly show that these patients tended to have higher recurrence rates in relatively shorter periods. Therefore, this finding makes the close follow-up of such cases mandatory. A total of 53.8% of patients with positive family history did have more than two stone episodes at the same period which was significantly higher than the patients without any family history.

Separate evaluation of both sexes clearly showed that male gender was associated with higher number of stone episodes which might be caused by an earlier onset of the disease in that gender, possibly also associated with an increased biochemical risk. This finding has also been found to be in accordance with the data of many studies regarding the recurrence rates which in turn may emphasize the potential inhibitory role of female hormones in urinary stone formation [25, 26].

In the light of all these findings, the higher incidence of recurrences and the early onset of the disease in patients with family history of urolithiasis may lead the clinicians

focus on genetic factors playing an important role in such patients as well as families.

One obvious limitation of our study is the lack of 24-h urine chemistry data. On the other hand, the retrospective nature of the study constitutes a minor limitation in our opinion. However, considering the limited number of the studies carried out so far and the problems in collecting data from the patients for such evaluations (i.e. follow-up of patients with respect to keeping them under dedicated medical therapy) may make a prospective study more difficult for the physicians working in this field of urology.

Conclusions

In the light of the multifactorial nature of urolithiasis, our findings show that in addition to dietary and lifestyle factors, a positive family history may also affect the onset as well as the course of urinary stone disease. Early onset of urinary stone formation along with the frequent stone episodes in such cases may make the positive family history predictive of the course of the stone disease and, therefore, these patients should be followed up closely to prevent future recurrences. We also believe that as an important epidemiological factor, a positive family history will add a new perspective to the evaluation and management of patients with urinary stone disease. This might be of particular value for those with severe recurrent stone formation.

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