

Pattern of family history in stone patients

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Abstract Genetic predisposition to urolithiasis is a much discussed topic. The objective of this paper is to identify the types of family members of proved urinary stone patients, who have a history of urinary stone formation. The study population consisted of 2,157 urinary stone patients interviewed in 2003–2007 in the urinary stone clinic. Family members with stone history were classified as group 1—first order single (one person in the immediate family—father, mother, siblings, or children), group 2—first order multiple (more than one member in the above group), group 3—second order single (one person in the blood relatives in family—grandparents, grandchildren, uncles, aunts, cousins, etc.) and group 4—second order multiple (more than one member in the above group). Of the 2,157 patients studied, 349 patients gave positive history of stone disease constituting 16.18%. Of these, 321 were males and 28 were females. Subdivision of the family members showed that 282 patients (80.80%) had single family member with stones and the rest 67 (19.20%) had multiple family members with history of stone disease. Group 1 which constituted one family member in the immediate family had

255 involvements (father: 88, mother: 16, brother: 135, sister: 2, son: 10, and daughter: 4); Group 2 with multiple members in the immediate family constituted 51 relatives; of these, father and brother combination was the most common with 35 occurrences. Group 3 with one person in the distant relatives in family namely grandparents, grandchildren, uncles, aunts, cousins, etc. constituted 27 occurrences and Group 4 with more than one member in the distant family constituted 16 occurrences. It is concluded that single family member involvement was more than multiple involvements. Males predominated. Stone occurrence was more in the immediate family members than distant relatives. Brothers formed the most common group to be involved with stone disease. Study of stone risk in the family members should be centred on brothers and sons of stone patients.

Keywords Urinary stone · Aetiology · Family history · First degree relatives · Stone forming risk · Genetic factors

Introduction

The actual aetiology of urinary stone disease has not yet been clearly defined. It is hence not possible to identify which of the stone-forming patients are likely to develop recurrence in the immediate or delayed future. The treatment of stone disease has to be metabolically appropriate. The relevance of finding the aetiology of stone formation rests in identifying a preventive mechanism for the process of calculogenesis. Prevention entails identification of factors which are modifiable. However, in most of the centres, treatment is blindly followed by giving empirical drugs which may be inefficient or even harmful to the patient. Who should get appropriate chemoprophylactic advice is

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another issue which has not been solved. One has to recognize various factors which contribute to stone formation in any individual. Several factors have been hypothesized. Some of these may not be correctable and some of these may be correctable. It is in this context that genetic predisposition to urolithiasis is discussed.

Ljunghall et al. [1] mention that congenital anomalies are well known to run in families and that 40% of stone patients had first degree relatives affected by stone disease. In order to understand the possible pattern of inheritance and what genetic predispositions are likely to be affecting the possibility of recurrent stone formation in the human beings, one has to conduct a detailed study of the inheritance pattern of the individual who forms the stones. Family history has been widely studied by various authors [2–5]. Congenital metabolic abnormalities such as cystinuria, primary hyperoxaluria, and 2,8-dihydroxy adeninuria are recognized as causes for stone formation. Kidney stones develop more frequently in individuals with a family history of kidney stones than in those without a family history; however, little information is available regarding whether the increased risk is attributable to genetic factors, environmental exposures, or some combination [3]. Calcium nephrolithiasis, the commonest type of urinary stone has been reported to have a strong familial component. Allelic variation in the vitamin D receptor (VDR) gene has been suggested as a partial explanation of differential calcium absorption or excretion in these patients [6]. Hence, recognition of the presence of such familial component will stimulate investigations to identify possible metabolic influences. This will prompt rigid follow-up and achieve successful prophylaxis.

Lee et al. [4] recognized that combination of father and mother having stone disease contributed to stone formation in significant numbers. Unfortunately, in depth study of the different types of family members who have been affected with stone disease has not been detailed in most of the studies. Such a detailed study is expected to give a clear picture of the inheritance pattern of the stone disease in families. This paper has attempted to identify the different family members of the proved urinary stone patients who have predisposition to have familial incidence of stone disease.

Materials and methods

2,157 patients with proved urinary stone disease were interviewed in the urinary stone clinic from 2003 to 2007. Patients who reported to have a positive family history were studied in further detail to identify the details of familial occurrence using a special chart (Table 1). The positive family history was classified as Group 1—first order single (one person in the immediate family—father,

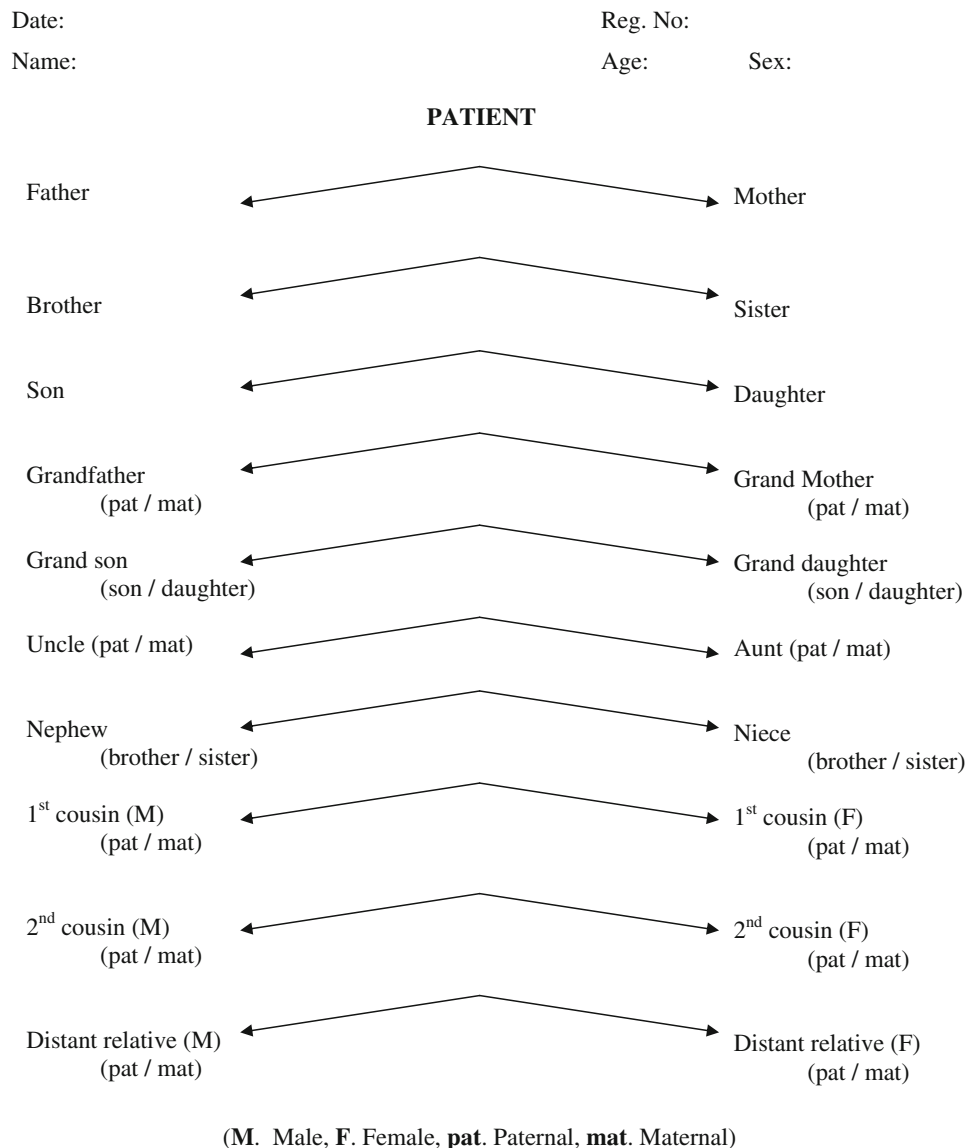
mother, siblings, or children), Group 2—first order multiple (more than one member in the above group), Group 3—second order single (one person in the blood relatives in family—grandparents, grand children, uncles, aunts, cousins, etc.) and Group 4—second order multiple (more than one member in the above group).

Results

Of the 2,157 patients studied, 349 patients gave positive history of stone disease constituting 16.18%. Of these, 321 were males and 28 were females (Table 2). Subdivision of the family members based on the sex of the patient and the primary or recurrent nature of stone disease (Table 3) showed that 282 patients (80.80%) had single family member with stones and the rest 67 (19.20%) had multiple family members with history of stone disease. Detailed assessment of the involved family members classified into the first degree, second degree, and third degree relatives (Table 4) showed that 376 first degree relatives of 306 urinary stone patients, 51 second degree relatives of 28 patients, 31 third degree relatives of 12 patients, and 6 distant relatives of 3 stone patients had positive stone history. Group 1 which constituted one family member in the first degree relatives had 255 involvements (father: 88, mother: 16, brother: 135, sister: 2, son: 10, and daughter: 4). Group 2 with multiple members in first degree relatives constituted 51 involvements. Of these, father and brother combination was the most common with 35 occurrences. Group 3 with one person in the second degree, third degree or distant relatives in family namely grandparents, grand children, uncles, aunts, cousins, etc. constituted 27 occurrences and Group 4 with more than one member in the distant family constituted 16 occurrences.

Discussion

Recurrence of stone disease has been very high in several populations with stone disease. It has not been possible to recognize which of the patients have been developing recurrences more often than the others. It has been suggested that a familial tendency may be one of the factors for increased recurrence in stone patients [7]. About one-third of the patients with urinary calculi had a positive family history [5]. In order to recognize which patients were likely to form recurrences more frequently, several studies have been undertaken by different authors in different places to identify the various reasons for increased recurrence. Identification of the positive family history particularly in the first degree relatives was an outcome of such studies. Curhan et al. [3] have found that the increased recurrence is

Table 1 Pattern of recording positive family history**URINARY STONE PATIENT – FAMILY HISTORY TREE****Table 2** Occurrence of family history in stone patients—sex-wise

Sex	FH +ve	FH –ve	Total
Male	321	1,615	1,936
Female	28	193	221
Total	349 (16.18%)	1,808 (83.82%)	2,157

associated with positive history of stone disease. A family history of stones was significantly more common among the stone formers than among the controls, largely due to an increased frequency of stones among the fathers and brothers of the proposti [2].

Ljunghall et al. [1] reported that positive family history was more in females compared to the males. However, the present study showed positive family history to be more in males compared to females (16.58% vs. 12.66%). Ljunghall et al. [1] also recognized that fathers were more involved positively in stone disease than the mothers. This was seen to be the case in present study also. However, in the present study, it was seen that the maximum number of family members involved was among brothers 50.53% followed by the fathers 35.37%, mothers 6.12%, son 4.63%, sister 1.86% and daughter 1.60% among the first degree relatives. In the present study, it was seen that the percentage of involvement of family members was more in the

Table 3 Primary and recurrent stone disease in relation to family history

	Male				Female				Total
	Primary		Recurrent		Primary		Recurrent		
	FH +ve	FH −ve	FH +ve	FH −ve	FH +ve	FH −ve	FH +ve	FH −ve	
Single	33	426	236	1,189	4	88	9	105	2,157
Multiple	14		38		2		13		
Total	47		274		6		22		
Total	473		1,463		94		127		
Grand total	1,936				221				

Table 4 Incidence of family history in different degrees of relatives

No.	Relation	Single			Multiple			Total
		Male	Female	Total	Male	Female	Total	
First degree relative								
1	Father	88	×	88	45	×	45	133
2	Mother	×	16	16	×	7	7	23
3	Brother	135	×	135	55	×	55	190
4	Sister	×	2	2	×	5	5	7
5	Son	10	×	10	7	×	7	17
6	Daughter	×	4	4	×	2	2	6
	Total	233	22	255	107/46	14/5	121/51	376/306
Second degree relative								
7	Pat. grand father	2	×	2	2	×	2	4
8	Mat grand father	×	×	×	1	×	1	1
9	Pat grand mother	×	2	2	×	2	2	4
10	Mat grand mother	×	×	×	×	×	×	×
11	Grand son (son)	1	×	1	3	×	3	4
12	Grand son (daughter)	×	×	×	×	×	×	×
13	Grand daughter (son)	×	1	1	×	2	2	3
14	Grand daughter (daughter)	×	×	×	×	×	×	×
15	Pat. uncle	3	×	3	8	×	8	11
16	Pat. aunt	×	2	2	×	3	3	5
17	Mat. Uncle	4	×	4	7	×	7	11
18	Mat. aunt	×	1	1	×	3	3	4
19	Nephew (brother)	1	×	1	2	×	2	3
20	Nephew (sister)	×	×	×	×	×	×	×
21	Niece (brother)	×	1	1	×	0	0	1
22	Niece (sister)	×	×	×	×	×	×	×
	Total	11	7	18	23/7	10/3	33/10	51/28
Third degree relative								
23	Pat. male cousin	2	×	2	3	×	3	5
24	Pat. female cousin	×	2	2	×	2	2	4
25	Mat. male cousin	3	×	3	11	×	11	14
26	Mat. female cousin	×	1	1	×	7	7	11
	Total	5	3	8	14/3	9/3	23/4	31/12
Distant relative								
27	Others	1	0	1	3/1	2/1	5/2	6/3
	Grand total	250	32	282	147/57	35/12	182/67	464/349

recurrent male stone formers compared to the primary stone formers. This distinction was more pronounced in the female stone formers.

The general observation that males are more prone to stone disease is projected in the present study also. The relationship between the increased incidence of stone disease in the males and the presence of increased positive family history in them compared to the females is not clearly elucidated so far. Higher frequency of stone history among the first degree relatives of stone patients compared to the relatives of controls has been reported [8]. This finding is confirmed in the present study also.

Further studies will have to be done to identify the different aspects of stone presentation namely age of onset of stone disease, the number of recurrences, the extent of crystalluria, the severity of pain, the stone episode rate, the biochemical correlations, urine microscopic correlations and the differences between the patients with and without positive family history, between those patients with single family member and multiple family members and between patients with involvement of first degree relatives and distant relatives.

Conclusions

It is concluded from the study that positive family history is an important risk for developing stones in any individual. Among the patients who attend the hospital for the first time, those with positive family history would have to be taken seriously as far as recurrence and prophylaxis are concerned. Single family member involvement was more

than multiple involvements. Males predominated. Stone occurrence was more in the immediate family members of the stone patients than distant relatives. Males predominated over the females in the family history. Brothers formed the most common group to be involved with stone disease. Study of stone risk in the family members should be centred on brothers and sons of stone patients. Male members with stone disease in the positive family history group will have to be carefully followed up for recurrences in future. Stone patients with brothers having stone disease will have to be taken care of maximum.

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