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ORIGINAL ARTICLE

FAMILY HISTORY AND BIOCHEMICAL DIAGNOSIS IN 1948 KIDNEY STONE FORMERS

ANTECEDENTES FAMILIARES Y DIAGNÓSTICO BIOQUÍMICO EN 1948 FORMADORES DE CÁLCULOS RENALES

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ABSTRACT

Introduction: The presence of family history of nephrolithiasis is associated with an increased risk of renal lithiasis. Different epidemiological studies have shown a family component in the incidence of it, which is independent of dietary and environmental factors. The role of heredity is evident in monogenic diseases such as cysti nuria, Dent's disease or primary hyperoxaluria, while a polygenic inheritance has been proposed to explain the tendency to form calcium oxalate stones. **Objective:** Our objective was to evaluate the family history of patients with renal lithiasis and the correlation of family history with its corresponding biochemical alteration, consi dering only those with a single metabolic alteration. **Methods:** a prospective and retrospective observational and analytical study that included 1948 adults over 17 years of age and a normal control group of 165 individuals, all evaluated according to an ambulatory protocol to obtain a biochemical diagnosis. They were asked about their family history of nephrolithiasis and classified into five groups according to the degree of kinship and the number of people affected in the family. **Results:** a positive family history of nephrolithiasis was found in 27.4% of renal stone formers, predominantly in women, compared to 15.2% of normal controls. The family history of nephrolithiasis was observed especially in 31.4% of patients with hypomagnesuria and in 29.6% of hypercalciuric patients. The rest of the biochemical alterations had a positive family history between 28.6% in hyperoxaluria and 21.9% in hypocitraturia. The highest percentage of family history of nephrolithiasis was found in cystinuria (75%) although there were few patients with this diagnosis. **Conclusions:** the inheritance has a clear impact on urolithiasis independently of the present biochemical alteration. Family history of nephrolithiasis of the first and second degree was observed between 21 and 32% of patients with renal lithiasis, with hypercalciuria and hypomagnesuria being the biochemical alterations with more family history.

KEYWORDS: renal lithiasis; family history; biochemical alterations

RESUMEN

Introducción: La presencia de antecedentes familiares de nefrolitiasis se asocia con un mayor riesgo de litiasis renal. Diferentes estudios epidemiológicos han mostrado un componente familiar en la incidencia de la misma, que es independiente de los factores dietéticos y ambientales. El papel de la herencia es evidente en enfermedades monogénicas como la cistinuria, la enfermedad de Dent

o la hiperoxaluria primaria, mientras que se ha propuesto una herencia poligénica para explicar la tendencia a la formación de cálculos de oxalato de calcio. **Objetivo:** Nuestro objetivo fue evaluar la historia familiar de los pacientes con litiasis renal y la correlación de los antecedentes familiares con su correspondiente alteración bioquímica, considerando solo aquellos con una única alteración metabólica. **Material y métodos:** Estudio observacional y analítico prospectivo y retrospectivo que incluyó a 1948 adultos mayores de 17 años y un grupo control normal de 165 individuos, evaluados todos siguiendo un protocolo ambulatorio para obtener un diagnóstico bioquímico. Se les preguntó acerca de su historia familiar de nefrolitiasis y se clasificó en cinco grupos según el grado de parentesco y el número de personas afectadas en la familia. **Resultados**: Se encontró historia familiar positiva de nefrolitiasis en el 27,4% de los formadores de cálculos renales, predominando en mujeres, frente al 15,2% de los controles normales. La historia familiar de nefrolitiasis se observó especialmente en el 31,4% de los pacientes con hipomagnesuria y en el 29,6% de los hipercalciúricos. El resto de las alteraciones bioquímicas tuvo antecedentes familiares positivos entre el 28,6% en la hiperoxaluria y el 21,9% en la hipocitraturia. El porcentaje más alto de antecedentes familiares de nefrolitiasis se encontró en la cistinuria (75%) aunque hubo pocos pacientes con este diagnóstico. **Conclusiones**: La herencia tiene un claro impacto en la urolitiasis independientemente de la alteración bioquímica presente. Se observan antecedentes familiares de nefrolitiasis de primer y segundo grado entre el 21 y 32% de los pacientes con litiasis renal, siendo la hipercalciuria y la hipomagnesuria las alteraciones bioquímicas con más antecedentes familiares.

PALABRAS CLAVE: litiasis renal; historia familiar; alteraciones bioquímicas

INTRODUCTION

Positive nephrolithiasis family history (NFH) is associated with an increased risk of urinary stone disease. Epidemiological studies have shown a familial component in the incidence of stone disease that is independent of dietary and environmental factors.[1] Several studies have been published about family history and risk of urolithiasis.[2-6] Recently Guerra et al.[7] in northern Italy, find an association between idiopathic cal cium nephrolithiasis and family history of kidney stone formers, they conclude that family history seems to be associated to an earlier idiopathic calcium nephrolithiasis onset in both genders and to a more complicated illness development, with higher prevalence of recurrence, bilateral stones, retained stones and need for urological procedures. Not only genetic and environmental factors, but also metabolic ones are implicated in the pathogenesis of stone formation.[8-9] The role of inheritance is obvious in monogenic diseases such as cystinuria, Dent's disease and primary hyperoxaluria,[10] but there is a clear familial tendency in idiopathic stone formation as well,[11] although genes involved are currently unknown. A polygenic inheritance has been proposed to account for the tendency to calcium oxalate stone formation in families.[12] Marickar et al.[13] evaluated nephrolithiasis family history (NFH) in patients with kidney stones divided into 4 groups accor ding to the degree of kinship and number of people affected in the same family. Nevertheless, they did not evaluate family history according to the biochemical abnormality present in the stone former. The aim of our paper is to assess family history of kidney stone former patients and the correlation with their corresponding biochemical abnormality.

METHODS

This is a mixed (prospective and retrospective) observational and analytical study that included 1948 consecutively adult patients above 17 years of age. They were selected from a database of kidney stone formers that were referred to our institution for metabolic evaluation from 2005 to 2014.

As inclusion criteria, all patients should fill in a form with questions about kidney stone family

history, besides their personal and family health history. In case of misunderstanding or lack of data, they were contacted to clarify them. We included a group of 165 age-matched normal controls (NC) without kidney stone history all of them stone free in an ultrasound scan performed for check-up reasons. These normal controls filled in the same form kidney stone formers did.

Positive kidney stone family history in patients with kidney stones and in normal controls was classified in five groups, Group 1: first order single, one kidney stone former 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 kidney stone former in a relative such as grandparents, grandchildren, uncles, aunts, cousins, Group 4: second order multiple, (more than one member in the above group) and Group 5: patients with a family history of kidney stones, that could not recall who the affected relative was.

Informed consent was obtained from all participants included in the study.

As we know biochemical abnormalities may be multiple or single but in this study we wanted to show nephrolithiasis family history in those with a single biochemical abnormality.

Thus, our population of 1948 kidney stone formers was consecutively chosen presenting one single biochemical abnormality. It is important to remark that in case of not obtaining a biochemical diagnosis, meaning a study with normal parameters, no metabolic abnormality (NMA) was considered as a diagnosis itself. Following the same criteria we considered hyperuricemia as a biochemical diagnosis in absence of any other biochemical abnormality. Consequently, we decided to include in our study both patients with hyperuricemia and those that could not show a metabolic abnormality in their biochemical evaluation.

We performed the biochemical studies in adult patients free from pediatric illnesses and severe hereditary conditions such as primary hyperoxaluria. Almost all of our patients were white caucasian as most of the population found in Argentine big cities.

Nephrolithiasis was confirmed by radiological, ultrasound, or computed tomography, or by spontaneous or surgically elimination of the stone. Kidney stone formers were evaluated at least 1 month after the symptomatic kidney stone or no longer than 12 months since the last episode, all of them urinary infection free. Patients with creatinine clearance less than 60 ml/min, (corrected to 1.73 m^2 of body area), were excluded as well as those with prolonged immobilization or receiving drugs that affect bone metabolism such as corticoids, diuretics, and anticonvulsants.

All kidney stone formers included in the study were evaluated following an ambulatory protocol in which the patients were asked to continue their usual diet and fluid entry.

To reduce bias, two consecutive-day urine collections in different recipients were obtained to calculate a mean value of each biochemical determination. These two 24-h urine samples were called periods A and B and kept in plastic recipients refrigerated with no additives. When the patient arrived to our institution, a fasting blood sample was obtained and urinary sediment and pH were measured in a fresh urine sample.

Nephrocalcinosis and medullary sponge kidney were not considered nor ruled out in our study.

In all samples, blood and urine several biochemical measurements were performed with the following technics. Serum calcium was measured with ion specific electrode, (ISE), with a 6 Synchron CX3 automated analyzer (Beckman, Beckman Instrumalets, Inc. Brea, California, USA). The same method was performed for urine calcium using an acidified aliquot. Serum ionic calcium was measured by ion-specific electrode with Roche Instrumalet Diagnostic 4 AVL without correction to pH (normal value 4.5–5.2 mg/dl). Both serum and urine creatinine (Jaffe) and phosphorus (UV) were measured using automated analyzer Spectrum CCX (Abbot Labs USA). Urine magnesium was measured with Synchron Systems (calmagita) reactive with an automated analyzer Synchron CX4. Both blood and urine

sodium and potassium were measured with automated analyzer CX3. Uric acid was measured in alkalized aliquot to avoid precipitation, with uricase reaction. Urine citrate determination was done by enzyme action using reagents of Sigma-Aldrich Corp. (St. Louis, Missouri, USA). Urine oxalate, using acidified aliquot, was measured by enzyme action, (Trinity Biotech, Co.Bray, Wicklow, Ireland). A pH electrode was used to measure urine pH in period C as soon as it was collected. Cystine determination in urine samples was performed with Brand chemical reaction. Intact serum parathyroid hormone, iPTH was measured with IRMA in those patients with at least two determinations of high total and ionic serum calcium, to rule out hyperparathyroidism.

Normal values were obtained in extra 84 non-kidney stone formers following the same protocol taken from our registry. Idiopathic hypercalciuria (IH) is considered as urine calcium more than 300 mg/24 h for male and 220 mg/24 h for female or more than 4 mg/kg in either sex, hyperuricosuria (HU) as more than 800 mg/24 h and 750 mg/24 h in male and female respectively, or more than 600 mg/l of urine, hypomagnesuria (MG) as less than 60 mg/24 h, hyperoxaluria (OX) as more than 45 mg/24 h, and hypocitraturia (CIT) as less than 350 mg/24 h. Persistent acid urine pH "Unduly acidic urine pH" (UAU) was considered when urine pH was less than 5.5, at least two times the same day. Cystinuria (CYS) was considered when its value was more than 250 mg/24 h. Hyperuricemia (HUS) was defined as more than 6.5 mg/dl in female and 7 mg/dl in male. Low urine volume (LUV) was assumed when it was less than 1000 ml/24 h.

Subtypes of idiopathic hypercalciuria, (absortive, fasting, renal or related to renal phosphate leak) were not considered.

We performed a bibliographic search in PubMed and Lilacs using as key-words: kidney stone formers, nephrolithiasis, urolithiasis, biochemical diagnosis in urolithiasis or nephrolithiasis and family history in kidney stone formers.

STATISTICAL ANALYSES

Statistical analysis for continuous variables was carried out using the Student test and Rank sum test Wilkonson for those variables that were not normally distributed. Categorical variables were analyzed with the Test two-sample proportion or the Fisher exact test. Statistical significance was considered at $p < 0.05$. Statistical analyzes were performed with the program Statistix 7.0.

RESULTS

Table 1 shows demographic characteristics in both total kidney stone population and normal

Table 1. Demographic characteristics in kidney stone (KS) patients and normal controls (NC) and gender distribution (F/M)

	KS (n=1948)	NC (n=165)	p	KS (F=970)	NC (F=105)	p	KS (M=978)	NC (M=60)	p
Age (years)	44.8 ± 13.4	42.1 ± 17.7	0.055	43.7 ± 13.7	44.0 ± 18.0	0.83	46.0 ± 12.9	44.7 ± 17.0	0.17
Weight (kg)	73.0 ± 16.0	70.3 ± 14.4	0.03	64.4 ± 13.6	64.7 ± 11.3	0.81	81.5 ± 13.6	79.4 ± 14.5	0.26
Height (m)	1.66 ± 0.09	1.67 ± 0.09	0.71	1.60 ± 0.06	1.62 ± 0.06	0.001	1.73 ± 0.07	1.74 ± 0.07	0.19
BMI (kg/m^2)	26.3 ± 4.9	25.2 ± 4.0	0.002	25.2 ± 5.3	24.6 ± 4.0	0.17	27.3 ± 4.3	26.1 ± 3.8	0.04

F: women; M: male

control group. From the total sample of 1948 kidney stone formers 978 were men and there were 970 women. In the control group, n=165, 65 were men and there were 100 women.

Female stone formers are 43.7 ± 13.7 years of age and male are 46.0 ± 12.9 years of age (p = 0.04). Stone formers were heavier (p<0,05) and had greater Body Mass Index (p<0.01) than normal controls. Kidney stone formers mean creatinine clearance was 105.9 ± 24.5 ml/min (female: 104.3 ± 24.8 ml/min, male: 107.5 ± 24.0 ml/min). **Table 2** shows from the total kidney stone population, n=1948, 27.4% (n=535) with positive NFH while in normal controls only 15.2% (n=25) have positive NFH (p<0.001).

Table 2. Positive nephrolithiasis family history in kidney stone (KS) patients and in normal controls (NC) according to gender

Positive NFH	KS (n=1948)	NC (n=165)	p
TOTAL	27.4%	15.2%	<0.001†
Female	30.0%	16.2%	<0.005†
Male	24.9%	13.3%	<0.05†

† Two-sample proportion test

Female kidney stone formers with NFH were 30% (n=291) while NFH was only 16.2% (n=17) in female normal controls n=105 (p<0.01). From the total male kidney stone formers n= 978, 24.9% (n=244) had positive NFH while there were 13.3% (n=8) in male normal controls n=60 (p<0.05).

Table 3 shows positive NFH according to the proposed 5 groups (I to V) in all kidney stone formers and sex distribution. Group 1 had the most NFH followed by Group III. In both groups female population predominated, p<0.01. In Group V, those who could not tell who the relative affected was, we found a total of 8.6% with positive NFH, female 9.5% male 7.8% with no statistical significance (p=0.48).

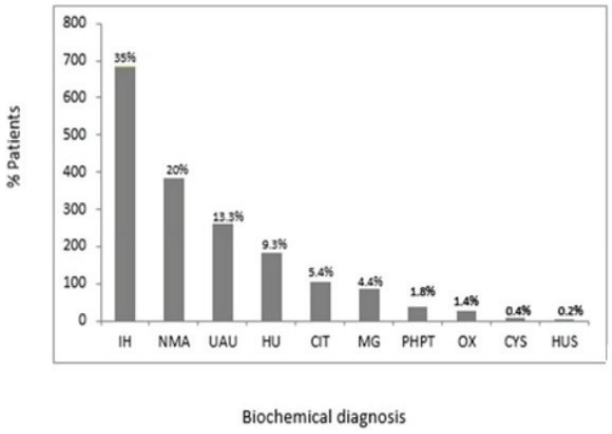
Table 3. Positive NFH groups in kidney stone (KS) patients and sex distribution

NFH n (%)	All KS (n=1948)	Female (n=970)	Male (n=978)	p
Total group	535 (27.4)	291 (30.0)	244 (24.9)	0.01
Group I	281 (52.5)	147 (50.5)	134 (54.9)	0.37
Group II	25 (4.7)	15 (5.1)	10 (4.1)	0.31
Group III	78 (14.6)	50 (17.2)	28 (11.5)	0.01
Group IV	16 (3.0)	8 (2.7)	8 (3.3)	0.99
Group V	135 (25.2)	71 (24.5)	64 (26.2)	0.18

p correstponds to Two-sample proportion test, comparing female/male

Figure 1 shows single biochemical diagnosis present in our total kidney stone population, n=1948. We found 35% (n=682) idiopathic hypercalciuria, with a clear predomination in female population 47.1% vs male 23% p<0.001. No metabolic abnormality was present in 20% (n=383) and low urine volume in 8.8% (n=171). Male population had a significant predomination in unduly acidic urine pH and hyperuricosuria (p<0.0001 for both diagnosis). Five patients had hyperuricemia as unique possible stone formation cause.

Figure 1: Biochemical diagnosis in patients with kidney stones



IH: IDIOPATHIC HYPERCALCIURIA, NMA: NO METABOLIC ABNORMALITY, UAU: UNDULY ACIDIC URINE pH, HU: HYPERURICOSURIA, CIT: HYPOCITRATURIA, MG: HYPOMAGNESURIA, PHPT: PRIMARY HIPERPARATHYROIDISM, OX: HYPEROXALURIA, CYS: CYSTINURIA, HUS: HYPERURICEMIA

Table 4 shows biochemical diagnosis more frequently present in kidney stone formers with positive NFH.

Except for cystinuria, present in few patients with 75% positive NFH, hypomagnesuria was the biochemical abnormality more frequently present in 31.4% kidney stone formers. Idiopathic hypercalciuria followed with 29.6% (female 32.6%, male 23.6%, p=0.01). No significant changes between male and female were found in the other biochemical abnormalities measured. Those with low urinary volume diagnosis, n=171 have 24.6% positive NFH (female 26% male 22.7%, p=0.51).

Table 4. Biochemical diagnosis and positive NFH

Diagnosis	**Positive kidney stone family history**			
n = 1948	All (n=535)	FEMALE	MALE	p
MG (n = 86)	31.4%	34.9%	21.7%	0.24
IH (n = 682)	29.6%	32.6%	23.6%	0.01
OX (n = 28)	28.6%	14.3%	33.3%	0.63
NMA (n = 383)	27.4%	30.1%	25.3%	0.30
HU (n = 182)	25.8%	18.2%	26.9%	0.38
AUA (n = 262)	25.2%	32.6%	25.6%	0.84
PHPT (n = 36)	25%	26.3%	23.5%	0.99
CIT (n = 105)	21.9%	20%	23.1%	0.71
CYS (n = 8)	75%	66.7%	100%	0.99

MG: HYPOMAGNESURIA, IH: IDIOPATHIC HYPERCALCIURIA, OX: HYPEROXALURIA, NMA: NO METABOLIC ABNORMALITY, HU: HYPERURICOSURIA, UAU: UNDULY ACIDIC URINE pH, PHPT: PRIMARY HIPERPARATHYROIDISM, CIT: HYPOCITRATURIA, CYS: CYSTINURIA

DISCUSSION

During the past 25 years, numerous reports have suggested that the frequency of kidney stone disease in western societies has been rising.[14-15] An estimate of lifetime risk in Europe is between 5 to 12% as well as in USA, affecting 13% of male and 7% of female in general populations.[14,16] In our country, taking into account subjects over 19 years of age, disease prevalence rate is 5.1%, in male 6.0% (CI 3.4%-8.6%) and in female 4.5% (CI 2.6%-6.4%).[17] Genetic or environmental factors or their combination predispose to stone formation.[18] Because some stone-forming conditions have a genetic predis-

position, a careful nephrolithiasis family history report should also be obtained.[4] The first demonstration that kidney stone family history increases the risk of nephrolithiasis dates to 1968.[19] The risk of becoming a stone former is more than 2.5 times greater in individuals with a positive family history of stone disease compared with those with no nephrolithiasis family history.[4] Positive NFH has also been correlated with multiple recurrences.[3] In our study NFH in patients and normal controls was classified in five groups, one more compared to Marickar publication about kidney stone formers and positive NFH.[13] The prevalence of NFH was significantly higher in women than men (30% vs. 24.9%, $p<0.05$) similar to the description by Guerra et al.[7] but in the latter with higher percentages, (52% vs 43%).

Positive NFH in our series of 1948 stone formers was 27.4%, with a mean age of 41.7 years of age, equal to the 27.5% described by Koyuncu et al.[2] in 1595 kidney stone formers with 44.8 mean years of age. Also similar to us Curhan et al. present a 25% positive family history in stone formers.[4] Our result was significantly higher compared to the 15.2% found in our 165 normal controls, with 42.1 years of age. In our population positive NFH was 1.8 times more frequent in kidney stone formers than in normal controls. Surprisingly in Trivandrum, India only 16.2% have positive NFH from 2157 kidney stone former patients, same percentage that we found in our normal controls.[13] Difficult to explain is the marked difference seen in our series with positive NFH in 30% of female and 24.9% of male compared to 1.3% female and 14.9% male described in Marickar et al. series.[13] Demographic and cultural factors may explain these differences, and in our country, diet habits with more animal proteins consumption might be an explanation. Other publications confirm our results, showing positive NFH in 17-37% of patients with stone disease and in 4-22% of normal healthy controls.[3,20]

In our series 67.1% (359 patients) belonged to Groups I and III (nephrolithiasis present in one first or second degree relative), whereas Marickar et al describe a higher prevalence (80.8%).[13] In Groups II and IV (nephrolithiasis in more than one first or second degree relatives) we found 7.7% (41 patients) highly different from the 19.2% described by the same authors. Separately are considered patients in Group V (n=135), those with positive NFH but no precision of the affected relative. We considered this group very important and its mentioning mandatory as it represented 25.2% of total sample with positive NFH.

From total metabolic diagnostic risk factors found in 1948 kidney stone formers idiopathic hypercalciuria predominated 35% (47% female and 23% male), similar to other series,[7,10,21-23] unduly acidic urine pH, hypomagnesuria, hypocitraturia and hyerpuricosuria followed as more frequent risk factors.

Positive NFH was more frequent in patients with hypomagnesuria and idiopathic hypercalciuria. Guerra et al.[7] describe higher predominance of idiopatic hypercalciuria with positive NFH in 2080 kidney stone formers, but these authors only evaluate first and second degree of positive NFH in idiopathic calcium nephrolithiasis.

Other authors without making divisions in NFH, find that half of the hypercalciuric population have positive NFH.[24] NFH was present in 25.2% of patients with UAU, and in 25.8% of hyperuricosuric patients mostly male, the latter similar to 20-25% described by Walker et al. in 666 male stone former patients with hyperuricosuria.[25] Cystinuria has positive family history in 75% of patients, quite different to only 34% of positive NFH in 76 cystinuric patients published by Rhodes et al.,[26] this difference might be related to the small number of cystinuric patients in our present series. We include five kidney stone former patients with hyperuricemia as the only diagnosis possible related to their nephrolithiasis that did not have positive NFH. Sex distribution was different according to biochemical diagnosis but due to small numbers we could not find statistical

significance in this biochemical abnormality. Hyperuricemia is not an evident cause of nephrolithiasis but some authors believe that its association to gout and to metabolic conditions with insulin resistance might reduce tubular ammonium production enhancing urine acidification and consequently stone formation.[27-28]

In spite of the intensive search, no other publications were available to compare with our study.

Among the limitations of this study we did not consider genetic abnormalities, molecular biology studies, diet habits and geographic areas.

Our study was designed to determine the existence of nephrolithiasis in relatives of kidney stone formers with a single metabolic abnormality. Future aims are to consider NFH in those kidney stone formers with multiple biochemical abnormalities as well as to evaluate biochemical diagnosis in relatives of our kidney stone former population.

CONCLUSIONS

This paper only considered those stone formers with only one metabolic alteration present in their evaluation; those with multiple metabolic alterations were excluded. That was thought to be more accurate in the conclusions about heredity**.**

In our present series positive NFH in stone formers is almost twice than that present in normal controls. Even those stone former patients with no metabolic abnormality or low urine volume have more NFH than controls. Most positive NFH belongs to Groups I and III, only one relative with positive NFH.

Considering all biochemical diagnosis found in our studied kidney stone population we observe idiopathic hypercalciuria, hypomagnesuria and hyperoxaluria as the biochemical diagnosis that have more proportion of positive nephrolithiaisis family history with a clear female predominancy.

Unduly acidic urine pH, hyperuricosuria, hypocitraturia, and primary hyperparathyroidism have similar positive nephrolithiasis family history. This study mainly focused in biochemical alterations present in the serum-urine protocol and their family history.

After an intensive bibliographic search, we consider our present study as the first one that states a relationship between type and number of relatives with nephrolithiasis in kidney stone formers and their corresponding single biochemical diagnosis.

Conflicto de intereses: Los autores declaran no poseer ningún interés comercial o asociativo que presente un conflicto de intereses con el trabajo presentado.

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