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Sponge kidney and renal lithiasis

ABSTRACT

Introduction: Sponge kidney is a renal malformation, of the collecting tubules, usually associated with nephrocalcinosis or distal tubular acidosis. The association with renal lithiasis is observed in 4-20%. **Objective:** The aim of our study was to describe biochemical risk factors for renal lithiasis in patients with sponge kidney. **Material and methods:** A retrospective, observational, cutoff study was performed between 2000 and 2017 where 37 patients with sponge kidney and renal lithiasis (26 females and 11 males) aged 37.3 ± 13.2 years were studied. The diagnosis of sponge kidney was made by excretory urogram. **Results:** Nephrocalcinosis was observed in 95%. The most frequent biochemical diagnosis was idiopathic hypercalciuria, which as the only and associated alteration was observed in 59.4%. Hyperuricosuria was the second diagnosis found in 32.4% (sole and associated) followed by hypocitraturia, hypomagnesuria and persistently acidic pHu. In men it was noteworthy that 46.2% did not present biochemical alteration. **Conclusions:** In conclusion, the relatively frequent association of sponge kidney and renal lithiasis stands out. Idiopathic hypercalciuria was the most frequent metabolic alteration as a cause of lithogenesis, followed by hyperuricosuria, similar to that described in the literature, although in a smaller proportion. Other alterations, such as hypocitraturia, hypomagnesuria and persistently acidic pHu should also be considered in the study of these patients.

KEYWORDS: sponge kidney; renal lithiasis; biochemical alterations; renal malformations.

INTRODUCTION

Medullary sponge kidney, renal spongiosis or Cacchi-Ricci disease (SR), is a common but poorly recognized cause of renal lithiasis.(1) It is a renal malformation, usually manifested by nephrocalcinosis and recurrent renal lithiasis, although other disorders may be present, such as alterations in renal acidification and concentration and pre-calcific ectasia.(2) Incomplete distal tubular acidosis (DTAA) is very frequent in patients with RE (33% to 40% of cases).(3-4) Idiopathic hypercalciuria is observed in 30-50%,(5) while associated with hypocitraturia and ARTd it is more common in pre-calcific cystic anomalies of the Bellini ducts that favor stone production. (6) The presence of hypercalciuria and ARTd may favor bone loss.(8) The association of renal lithiasis with RE varies between 4% and 20% according to different series.(7-8) The aim of the following work is to evaluate biochemical alterations in patients with sponge kidney.

MATERIAL AND METHODS

An observational, analytical, cross-sectional study was performed, where 37 patients with sponge kidney were retrospectively selected from our base of renal lithiasis, from 2000 to 2017. All were referred for biochemical study of their nephrolithiasis. The diagnosis of renal lithiasis was confirmed by the presence of renal calculi on radiography, renal ultrasonography, urotomography and/or spontaneous or instrumental elimination of the calculi. The diagnosis of sponge kidney was established by the presence of typical images in the excretory urogram and/or contrast urotomography. The presence of pre-calyceal papillary ectasia, with images in brush border or linear striae, radiating outwards from some or all calyces, documented in images taken at least 10 minutes after the injection of the contrast medium, without compression maneuvers and without signs of obstruction, was considered for the diagnosis. In enlarged pyramid films, intraductal concretions or cottony images may also be present in the calyces to a lesser or greater extent.

Patients with involvement of one or both kidneys were included. We defined nephrocalcinosis as the presence of intrarenal calcifications detected in radiographic studies.

Patients were evaluated at least one month after an episode attributed to renal lithiasis and at most 12 months after the episode, in the absence of infection or urinary obstruction. All patients were studied with an outpatient protocol for biochemical evaluation of renal lithiasis, following the usual diet and fluid intake. Two 24-h urine samples (period A and B) were collected and kept refrigerated in plastic containers with no preservatives added. A fraction of the last urine of period "B" was collected in the laboratory to determine urinary pH (pHu) and sediment analysis. Fasting blood was then drawn, 300 ml of distilled water was ingested, and then urine was collected from the subsequent 2 hours (period C). In all samples, including blood and the three urinary periods, biochemical measurements were performed with the following techniques: serum calcium, with an ion-specific electrode (ISE), using an automated analyzer 6 Synchron CX3 (Beckman, Beckman Instruments, Inc. Brea, California, USA). The same method was used for urinary calcium using an acidified aliquot. Ionic calcium was measured with a specific ion electrode with the Roche Diagnostic 4 AVL instrument, without correction for pH (normal value 4.5-5.2 mg/dl). Serum and urinary creatinine was measured with the Jaffé method and phosphorus (UV), in both cases using a Spectrum CCX automatic analyzer (Abbot Labs USA). Urinary magnesium was measured with a Synchron Systems reagent (calagite) with a Synchron CX4 automated analyzer. Sodium and potassium, in blood and urine, were measured with a CX3 automated analyzer. Uric acid, with alkalinized aliquots to avoid precipitation, was measured with the uricase method. Citrate in urine by enzymatic technique using Sigma-Aldrich Corp. reagents (St. Louis, Missouri, USA). Oxalate in urine, using acidified aliquots, was measured by enzymatic technique (Trinity Biotech, Co.Bray, Wicklow, Ireland). A pH electrode was used to measure pHu in period C. In case of a pHu < 5.5, the measurement was repeated, in a new urine sample to confirm the acidic pHu. Cystine in urine was qualitatively determined by Brand's reaction and quantified when positive. Since our protocol does not include a tubular acidification study, the diagnosis of tubular acidification was not considered in this series, although it was established during patient follow-up. With the values obtained in 84 normal controls of our registries, submitted to the same protocol, we defined: idiopathic hypercalciuria (IH) as calcium excretion higher than 300 and 220mg/day in men and women respectively, or higher than 4mg/ Kg of weight with normocalcemia and absence of other causes of hypercalciuria. Hyperuricosuria (UO) as excretion of more than 750 mg/24 h and 700 mg/24 h in men and women respectively, or more than 600 mg/L of urine, hypomagnesuria (MG) to excretion less than 60 mg/24 h, hyperoxaluria (OX) to more than 45 mg/24 h, and hypocitraturia (CIT) to less than 350 mg/24 h. The diagnosis of "persistently acidic pHu (UAU)" was established by the presence of two pHu< 5.5 and risk of uric acid crystallization in urinary saturation study. Cystinuria (CIS) is defined as cystine excretion > 250 mg/day. Low urinary volume (BVU) was considered when diuresis was less than 1000 ml/24 h. Two consecutive urine collections were obtained to calculate an average value for each biochemical determination, in an attempt to reduce any bias. Patients without defined biochemical alterations were considered as having no metabolic activity (MAR). Renal phosphate loss (PRP) was defined by a serum phosphorus lower than 2.8 mg/dl and a renal threshold (URP) lower than 2.4 mg/dl, normalized to a glomerular filtration rate estimated by creatinine clearance (TmPO4/GFR; normal range 2.5-4.2 mg/dl). Urinary saturation was calculated in most patients with a computerized program (ACTILIT), which evaluates the relative risk (RR) of crystallization of different salts. Of our patients with renal lithiasis and RE (37), we determined the chemical composition using the colorimetric method (visual comparison) and in the remaining 10% by optical crystallography with polarized light. As exclusion criteria we considered patients with creatinine clearance < 50 ml/min, who had urinary tract infection at the time of the study or who

were receiving medication that could affect the results. It should be noted that the age considered in this series was taken at the time of metabolic diagnosis of renal lithiasis.

All patients signed an informed consent form to handle their data, as is the norm in our institution.

The statistical analysis used the mean and standard deviation to express the excretion of the different analytes in the study population. Frequencies were used to express metabolic alterations. The tests used were: Student's t-test or kruskal Wallis for comparison of means and Chi-square and proportionality tests. A $p < 0.05$ was considered significant: The statistical program used was CSS 24: Statistica Software (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

Table 1 shows the total demo- graphical data (n=37) of patients with renal lithiasis and renal spongiosis, divided between women and men. We observed a predominance of women, ratio 2.4:1, with similar ages between sexes and obviously greater height, weight and BMI in men. Macro- or microhematuria was present in 17 of the 37 patients (46%). A history of urinary tract infection was found in 22 patients (59.5%) with no differences between women and men. Family history of renal lithiasis in the first degree (mother, father, siblings or children) was present in 13/24 (35%) and in the second degree (grandparents, grandchildren, uncles, aunts, cousins or nephews) in 1/34 (3%). Bilateral renal spongiosis was present in 28/37 (75.7%) and unilateral in 9/37 (24.3%). Nephrocalcinosis, present in radiographs or computed tomography and eventually in ultrasonography, was observed in 35/37 patients (95%) with different degrees of severity. If we discard ultrasonography (as a non-specific technique) nephrocalcinosis was present in 59.5% (n=22). Arterial hypertension was observed in 8/37 (22%). In 20 patients (54%) the composition of the calculus could be obtained. Calcium oxalate was present in 16/20 patients (80%), uric acid in 2/20 (10%), calcium phosphate in 1/20 (5%) and hydroxyapatite + struvite in 1/20 (5%).

Table 1. Demographic parameters of the population.

	Total patients n = 37	Women n. = 26	Men n = 11
Age (years)	37.3 ± 13.2	38.8 ± 11.9	33.8 ± 16
Weight (Kg)	67.9 ± 14.1	62.6 ± 12.5	80.2± 9.1
Size (m)	1.66 ± 0.1	1.62 ± 0.0	1.75 ± 0.5
BMI (weight/height2)	24.5 ±3.3	23.8 ± 3.6	26 ± 1.8

Table 2 shows the baseline biochemical parameters of the 37 patients, while **Table 3 shows** the single biochemical alterations in the total number of patients and **Table 4** shows the associated alterations. As can be seen, IH is the most frequent diagnosis, representing 59.4% of the total as a single or combined diagnosis.

Table 2. Baseline plasma biochemical parameters**.**

Blood parameters	**ER/renal lithiasis (n=37)**
Creatinine (mg/dl)	0.91 ± 0.16
	9.6± 0.2
Calcemia (mg/dl)	4.6± 0.8
Ionic calcium (mg/dl)	± 0.5
Phosphorus (mg/dl)	46.9 ± 16
iPTH (pg/ml) n=25	4.5 ± 1.5
Uricemia (mg/dl)	138 ± 14.3
Sodium (mEq/l)	4.2 ± 0.4
Potassium (mEq/l)	

Table 3. Unique metabolic alterations in 37 patients with sponge kidney and renal lithiasis.

Biochemical diagnostics	**N° patients**	**Percentage**
HI		35.1
UO		8.1
CIT		5.4
MG		5.4
UAU	1	2.7

Table 4. Associated metabolic alterations in 37 patients with sponge kidney and renal lithiasis**.**

Biochemical diagnostics	N° patients	Percentage
HI-UO		18.9
HI-CIT	1	2.7
HI-UAU	1	2.7
MG-UO	1	2.7
CIT-UO	1	2.7

The second most common single or associated disorder was hyperuricosuria, present in 32.45%. Hypocitraturia, hypomagnesuria and persistently acidic pHu shared 8.1% as single or associated alteration. Hypomagnesuria was found only in women, whereas hyperuricosuria predominated in men. Of note, the low number of men made gender comparison difficult.

No metabolic activity (SAM) was observed in 5 patients (13.5%). There were no patients with low urinary volume and the mean pHu was 5.9 + 0.5. Decreased URP was observed in three patients (8.1%) independent of the biochemical alteration they presented.

DISCUSSION

The main objective of this retrospective study was to evaluate metabolic alterations in patients with sponge kidney and renal lithiasis. Sponge kidney, or canalicular precalcific ectasia, is a common disorder characterized by tubular dilatation of the collecting ducts and formation of cysts confined to the medullary pyramids, especially in their internal portions8. In patients with renal lithiasis the association with ER varies between 4 and 20%,(7-8) while in individuals without renal lithiasis it ranges between 2%.(9) Its pathogenesis is still unclear and ranges from genetic alterations to an acquired condition secondary to obstruction of the collecting ducts by calcium crystals.(8) Some authors consider, however, ER as a congenital disorder,(10-11) which could be the result of a disruption at the interface of the "metanephric mesenchyme of the ureteric bud" probably due to disease-causing mutations or specific polymorphisms in the GDNF (*glial cell line derived neurotrophic factor)* genes and its receptor RET.(2,12-14) Finally the study of Fabris and Gambaro provide strong evidence that familial clustering of ER is common, and has an autosomal dominant inheritance with reduced penetrance and variable expressivity.(15)

Precalcific canalicular ectasia may involve one or more renal papillae in one or both kidneys. Idiopathic hypercalciuria, hypocitraturia, relatively high urinary pH and urinary stasis in the dilated papillary canaliculus trigger the formation of calcium phosphate and/or calcium oxalate stones.(2) Lesions are bilateral in 70% of cases(9) similar to 76% of those found in our series. It occurs in the same proportion in both sexes2 although in our series it clearly predominated in women with a 2.4:1 ratio. Age at diagnosis varies between 30-50 years,8 which coincides with 37.3 ± 13 years in our patients. The renal calculi observed in ER are oxalate and/or phosphate or other calcium salt9. This coincides with what was observed by us, that in 17 of the 19 stones that could be analyzed, calcium salts accounted for 89% and we only found uric acid stones in 2 patients (11%), with biochemical diagnoses of UAU and UO. Family history of first and second degree renal lithiasis was observed in 38% of our patients, much lower than the 68% described by Fabris et al.(6) in 65 patients with renal lithiasis and RE. The presence of hematuria (macro or micro) is relatively frequent,(11-12) we observed it in 46% of cases. Nephrocalcinosis is also common in RE,(16) in our series we observed it in 95% of cases. Among the biochemical alterations of renal lithiasis, idiopathic hypercalciuria predominated in our series in both women and men, in values similar to those described by Cameron et al.(17) (30-50%), and McPhail et al.(12) (58%) and clearly lower than the 100% described by Fabris et al.(7) Although a greater presence of hypercalciuria could be expected as a cause of calcium salt precipitation, due to impaired calcium reabsorption linked to damage to the collecting tubule, our data coincide with those of other authors(12,17) in the sense that other biochemical alterations could cause the precipitation of calcium crystals as observed in hypocitraturia, hyperuricosuria, UAU or hypomagnesuria, in addition to hypercalciuria. The

second alteration we found was hyperuricosuria (single or associated), while hypocitraturia together with hypomagnesuria (two crystallization inhibitors) were present in 8.1% of the cases, the latter being present only in women similar to that described in another series.(12) Persistently acidic pHu was only observed in 5.4%, similar to the data of Yagisawa et al.(18) It is noteworthy that in men no biochemical alteration was found in 46.3% of the cases, which represented more than twice as many as in women (18.9%). It is important to point out that in recent years the excretory urogram (gold standard) for the diagnosis of ER has lost its validity, so its diagnosis has markedly decreased, especially considering that helical computed tomography with intravenous contrast is not always requested in lithiasic patients and even fewer request enlarged films that may suggest the diagnosis.

The limitations of our study are the small number of male patients, which prevented a more accurate comparison with women, not including patients with distal tubulo renal acidosis, given its frequent association with RE and renal lithiasis. From the data presented we can conclude that the association of sponge kidney and renal lithiasis is relatively frequent and in the presence of multiple uni or bilateral lithiasis, and/or the presence of unspecific multiple renal calcifications, in the presence of renal colic, the diagnosis should be suspected. In contrast to what is described in the literature, in our series women predominated. Idiopathic hypercalciuria was the most frequent biochemical alteration, followed by hyperuricosuria and then hypocitraturia-hypomagnesuria. We have no explanation as to why no biochemical alteration was observed in half of the men. It is important to highlight that idiopathic hypercalciuria is not always the only metabolic alteration related to ER, so the study of other metabolic alterations should be considered.

Conflict of interest: The authors declare that they have no commercial or associative interests that would present a conflict of interest with the work presented.

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