

Nephrolithiasis-induced end stage renal disease

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Introduction: Nephrolithiasis still remains a too frequent and underappreciated cause of end stage renal disease (ESRD).

Methods and patients: Of the entire cohort of 7128 consecutive patients who started maintenance dialysis in our nephrology department between January 1992 and December 2006, a total of 45 patients (26 women, 19 men) had renal stone disease as the cause of ESRD. The type of nephrolithiasis was determined in 45 cases and etiology in 42. The treatment and evolution of stone disease and patient's survival were studied.

Results: The overall proportion of nephrolithiasis related ESRD was 0.63%. The mean age was 48.4 years. Infection stones (struvite) accounted for 40%, calcium stones, 26.67% (primary hyperparathyroidism: 15.56%; familial hypercalciuria: 4.44%, unknown etiology: 6.66%), primary hyperoxaluria type 1, 17.78% and uric acid lithiasis in 15.56% of cases.

The mean delay of the evolution of the stone renal disease to chronic renal failure was 85.8 months. The feminine gender, obesity and elevated alkaline phosphatases >128 IU/L were significantly correlated with fast evolution of ESRD. The median evolution to ESRD was 12 months. The normal body mass index (BMI), medical treatment of stone and primary hyperoxaluria type 1 were correlated with fast evolution to ESRD.

All patients were treated by hemodialysis during a mean evolution of 60 months. Sixteen patients died. The patient's survival rate at 1, 3 and 5 years was 97.6, 92.8 and 69% respectively. Hypocalcemia, cardiopathy and normal calcium-phosphate product were significantly correlated with lower survival rate.

Conclusion: Severe forms of nephrolithiasis remain an underestimated cause of ESRD. These findings highlight the crucial importance of accurate stone analysis and metabolic evaluation to provide early diagnosis and efficient treatment for conditions leading to ESRD.

Keywords: Nephrolithiasis, ESRD, struvite, dialysis, prevention

Introduction

The contribution of nephrolithiasis related to end stage renal disease (ESRD) in patients requiring renal replacement therapy has never been specifically evaluated. Nephrolithiasis still remains a too frequent and underappreciated cause of ESRD and this is all the most unfortunate since such prognosis is now preventable in most cases.

Infection stones, especially when bilateral developing a stag horn configuration are universally considered the most frequent cause of urolithiasis associated ESRD.^{1,2} Extensive stone development also has been observed with calcium-oxalate, uric acid or cystine stones and in patients with anatomic abnormalities of the urinary tract.³

In addition to the well known obstructive and infections mechanisms of kidney injury crystal deposition in the tubules and interstitium of both kidneys constitutes

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another, often underappreciated mechanism of progressive renal failure.

The potential risk of degradation of renal function justifies the etiological investigation of all lithiasis associated pathologies. Therefore calculus analysis of the crystalline phases and morphological characteristics is an important factor in the etiological diagnosis of the disease.

In the present study we reviewed the charts of all patients for whom urinary stone disease was recorded as the exclusive or preponderant cause of ESRD in the entire cohort of patients who started maintenance dialysis therapy at our nephrology department from 1992 to 2006. We analyzed: the frequency of nephrolithiasis associated ESRD; distribution of various types of nephrolithiasis; their respective cause; treatment; and evolution. We reviewed also patient survival rate at 1, 3 and 5 years. These results were then compared to data contained in the literature.

Patients and methods

Of the entire cohort of 7128 consecutive patients who started maintenance dialysis therapy at our nephrology department between January 1992 and December 2006, a total of 45 patients (26 women, 19 men) had renal stone disease as the cause of ESRD and constitute the patients in this study. In all 45 patients urinary stone disease was the exclusive or preponderant cause of ESRD assessed by means of a detailed patient history, renal biopsy and exclusion of other possible causes of interstitial nephropathy and renal insufficiency. The cause of stone disease was identified on the basis of history, laboratory data and urinary crystal examination.

Stones that developed in patients who were on dialysis therapy were not considered in our study. The Cockcroft and Gault equation was used in the assessment of creatinine clearance.

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Creatininemia } (\mu\text{mol/L})}$$

This product should be multiplied by 1.23 for men. A renal failure is defined by a creatinine clearance lower than 80 mL/minute and the end stage is retained if the creatinine clearance is lower than 10 mL/minute.

The statistical analysis was made using the Stat View Software 5.0. Categorical variables were compared using the unpaired student's T-test. Nominal variables were

compared using chi square. The patient's survival rates were compared using the actuarial method and comparison was performed using logrank test. The level of statistical significance was at 5%.

Results

The overall proposition of nephrolithiasis related ESRD among the total number of incident ESRD cases was 0.63% (ie, 45 of 7128 patients). Annual incidence was 3. Of the 45 patients, there were 19 men (42.22%) and 26 women (57.78%) with a gender ratio of 0.73.

The mean age of the patients was 48.4 ± 17.63 years (range of 17–80). The majority of patients (32) originated from the north and the north west of Tunisia, (74.11%); ie, 20 (44.44%) and 12 (16.67%) respectively. Eight patients originated from the central Tunisia (17.78%) and 5 from the south (11.11%).

Eleven patients had family antecedents of urinary lithiasis (24.45%) and six of primary hyperparathyroidism type 1. Twenty four patients had hypertension (53.33%), six had diabetes (13.33%) and four cardiopathy (8.89%).

The Table 1 illustrates the discovering circumstances of nephrolithiasis. The diagnosis of nephrolithiasis stemmed from painful symptomatology, hematuria or urinary infection and was confirmed by radiology (x-ray–tomography–urography). Morphoconstitutional analysis, supplemented by biochemical and metabolic evaluation of nephrolithiasis, confirmed the nature and etiology of calculi. Tables 2 and 3 illustrate the composition and the etiologies of nephrolithiasis.

Thirty one patients were treated surgically: 15 had a lombotomy with lithotomy; 10 a unilateral nephrectomy, 3 a percutaneous nephrolithotomy and 3 treated with extracorporeal lithotripsy. The 14 remaining patients were treated medically. The median of evolution of the nephrolithiasis from nephropathy to chronic renal failure (CRF) was 24 months

Table 1 Discovering circumstances of nephrolithiasis

Discovering circumstances	Number of patients	Percentage %
Renal colic	16	35.55
Fortuitous discovery (radiology)	8	17.78
Lithiasis Emission	5	11.11
Urinary infection	5	11.11
Macroscopic Hematuria	4	8.89
Kidney Failure	3	6.67
Others	4	8.89
Total	45	100

Table 2 Composition of lithiasis and nature

Composition	Number of patients	Percentage %
Struvite	18	40
Calcium lithiasis	12	26.67
Oxalic lithiasis	8	17.77
Uric acid lithiasis	7	15.56
Total	45	100

(range 1–408 months). The evolution to CRF was faster in men than women (68 versus 109 months, $P = \text{NS}$). The evolution of the condition in patients originating from the center of Tunisia rather than those from north (35.1 versus 124.8 months, $P = \text{NS}$) or North West (35.1 versus 72.7, $P = \text{NS}$). Patients with hypertension versus others without (59.1 versus 116.2 months $P = 0.08$) without any statistically significance. The condition was also significantly faster in the event of diabetes (19.3 versus 96 months, $P = \text{NS}$) or cardiopathy (18.75 versus 92.3, $P = \text{NS}$). Obesity defined by a body mass index (BMI) $\geq 30 \text{ kg/m}^2$ was correlated with a faster evolution to CRF (14.8 versus 99.7 months, $P = 0.03$).

The etiology of nephrolithiasis had no impact on this evolution. Surgical treatment slowed down the evolution of CRF compared to medical treatment (97 versus 61 months) without any statistically significance.

Alkaline phosphatases higher than 128 IU/L were significantly correlated with a faster evolution to CRF than those lower than 128 IU/L (57 versus 142.9 months, $P = 0.011$) No correlation was found with the other phosphocalcic parameters (calcemia – phosphate, calcium – phosphate product and parathormone).

The final stage of CRF was reached after a median evolution of 12 months (range 1–156 months). The age, gender and geographic origin had no significant impact on the evolution to ESRD. Obesity was significantly correlated to the evolution to ESRD (71 versus 18 months, $P = 0.015$).

The patients having a parathyroid hormone (PTH) between 150 and 300 pg/mL evolved more quickly to ESRD than patients having secondary hyperparathyroidism (19.66 versus 36.6 months, $P = \text{NS}$).

The nephrolithiasis etiology had no impact on the evolution to ESRD, nevertheless patients having primary hyperoxaluria type 1 evolved more quickly to ESRD than those having infectious (15.45 versus 31.7 months, $P = \text{NS}$) or calcic nephrolithiasis (15.45 versus 41.3 months, $P = \text{NS}$).

Table 3 Etiologies of nephrolithiasis

Etiology	Number of patients	Percentage %
Infectious lithiasis	18	40
Primary hyperparathyroidism	7	15.56
Familial hypercalciuria	2	4.44
Unknown calcic lithiasis etiology	3	6.66
Primary hyperoxaluria type 1	8	17.78
Uric acid lithiasis	7	15.56
Total	45	100

The medical treatment of the lithiasis was significantly correlated to a faster evolution to ESRD compared to urological treatment (8.75 versus 53.2 months, $P = 0.04$). All patients were treated by hemodialysis. The median duration of dialysis was 59 months (range 1–169 months). Osteoarticular complications occurred in 91.11% of patients (secondary hyperparathyroidism = 55.56% and adynamic bone disease in 35.56% of patients) and cardiovascular in 66.67% (cardiac failure: 22.22%, coronaropathy 20% and heartbeat rate disorders 22.3%).

Sixteen patients died. The Table 4 illustrates the causes of death. The patient's survival rate at 1, 2, 3 and 5 years was: 97.6%; 95%; 92.8%; and 69% respectively and this was 96%; 95.2%; 90%; and 71% for all dialyzed patients. Age, gender, geographic origin, hypertension, BMI had no impact on patient's survival or nephrolithiasis etiology. Patient survival at 5 years was significantly combined with cardiopathy (33% versus 72%, $P = 0.06$), hypocalcemia (56% versus 100%, $P = 0.014$), normal calcium phosphorus product (53% versus 92% $P = 0.0084$). The other phosphocalcic parameters had not any impact on patient survival. The faster evolution to the ESRD (≤ 31.5 months) was significantly correlated

Table 4 The causes of death

Cause of death	Number of patients	Percentage (%)
Sudden death	6	37.5
Septic shock	4	25
Acute pulmonary Edema	1	6.25
Hypokalemia	1	6.25
Cachexia	1	6.25
Stroke	1	6.25
Myocardial infarction	1	6.25
Tuberculous spondylodiscitis	1	6.25
Total	16	100

with longer survival at 7 years compared to slower evolution (>31.5 months).

Discussion

End stage renal disease caused by urinary stone disease, although accounting for a limited proportion of cases, still remains a problem that should not be overlooked.

The principal mechanisms involved in the development of renal failure in patients with nephrolithiasis were recurrent stone formation, obstruction of the excretory tract and extensive crystal deposition in the renal parenchyma. Irreversible renal impairment was observed essentially in patients with a delayed diagnosis, suboptimal urological and medical management, or intrinsically severe forms of stone disease.^{4,5} Severe forms of nephrolithiasis remain an underestimated cause of potentially avoidable ESRD and the need renal replacement therapy.⁶

In our experience, nephrolithiasis related ESRD contributed 0.63% to the total series of patients who started maintenance dialysis therapy at our department of nephrology during a 15 year period. These figures are in agreement with those extracted from recent the United States Renal Data System data. Among 228,332 white patients who started renal replacement therapy in the US from 1993 to 1997, a total of 1.5% were categorized as having “nephrolithiasis, obstruction, gouty” as the primary renal disease, thus leading to an estimated incidence of 2.9 patients/year. Paul Jungers and colleagues have reported that the overall proportion of nephrolithiasis related ESRD was 3.2%.⁶ Another estimation can be extracted from a prospective epidemiological inquiry conducted at all nephrology and dialysis units in the Ile de France area, which has a total population of 10.7 million inhabitants. Of 1060 adult patients who started maintenance dialysis therapy in 1998, nephrolithiasis was recorded as the cause of ESRD in 1.8% of cases.⁷ In a cohort of 171 patients with severe idiopathic calcium stone disease reported by Marangella and colleagues 18% had mild renal insufficiency but no patients reached ESRD during a mean follow up of 3.5 years.⁸ Of 2000 consecutive unselected stone formers reported by Gupta and colleagues only 33 patients (1.7%) had mild to moderate renal failure.⁹ A very low frequency of progressive renal failure was reported in other studies. Of 3266 patients with nephrolithiasis reported recently by Worcester and colleagues none developed ESRD and there was no significant decline in creatinine clearance between the first and the last visit.² Jungers reported that the frequency of nephrolithiasis related ESRD significantly

decreased with time; from an average proportion of 4.7% from 1989 to 1991 to 2.2% from 1998 to 2000.⁶

In our study, the rate of ESRD, due to nephrolithiasis, was the prerogative of the fifty years old adult patients with female prevalence. In a Moroccan study including 183 patients, Oussama and colleagues reported that the average age was 60 years with clear male prevalence.¹⁰ Coe and colleagues found the similar results.¹¹ The potential risk of degradation of renal function highlights the crucial importance of accurate stone analysis and metabolic evaluation to provide early diagnosis and the correct therapy for conditions that may lead to ESRD.

In our study, morphoconstitutional analysis of calculi from 45 patients showed that struvite was the main component in 40% of cases. In all these patients, disease onset occurred a long time ago, before the modern era of urological treatment. This cause of stones has been reported in other studies: Jungers in 36%⁶ and Gupta in 64% of cases.⁹

However many authors reported that the frequency of this cause will decrease in the future because of earlier diagnosis and easier urological management.¹² Struvite accounted for 15.3% of nephrolithiasis among 183 patients for Oussama and colleagues.¹⁰ The female prevalence noted in our series was also found by Gupta⁹ although not by Oussama.¹⁰

In children, Daudon and colleagues noted that struvite frequency was 9.9% of cases.¹³ Although responsible for ESRD in nearly 26.67% of our patients, calcium stones appear to be an infrequent cause of ESRD compared with the very large number of calcium stone formers. Its frequency was 26.7% for Jungers and even higher for Oussama in 58.5% of cases.^{6,10}

In our experience, such an outcome is mainly caused by late diagnosis in patients with primary hyperparathyroidism (58.83%) and idiopathic hypercalciuria (16.66%) resulting in multiple stone episodes; with the aggravating influence of recurrent urinary tract infection in several patients.

Among 12 calcium stones reported by Jungers, heavy hypercalciuria was present in 33% of cases, primary hyperparathyroidism in 16.66% and medullary sponge kidney in 41.67% of cases.⁶ In our study the etiology was not identified in 6.66% of cases. This frequency was much less than that of Gupta with 59% of cases.⁹

Uric acid nephrolithiasis accounted for 15.56% of cases in our study; however in western literature, it represented by 7.2% to 15.3% of cases.¹⁴⁻¹⁶ This figure was 17.8% for Jungers and 18% for Oussama.^{6,10} It does seem that this type of calculi is more frequent in North Africa than in Europe or US, suggesting the influence of nutritional factors.¹⁰

There was a male prevalence in our series and also for Oussama.¹⁰ Primary hyperoxaluria type 1 (PH1) is frequently misdiagnosed, especially when urinary stones manifest first in adult patients or if early symptoms are misinterpreted.⁶ It accounted for 17.78% of nephrolithiasis in our study. This frequency was largely higher than that of Jungers.⁶ A very low frequency of progressive renal failure especially ESRD was reported.

Of 3266 patients with nephrolithiasis reported by Worcester and colleagues none developed ESRD and there was no significant decline in creatinine clearance between the first and the last visit (2). In our experience, the evolution of nephrolithiasis nephropathy to chronic renal failure (CRF) was paradoxically very fast, with a median of 24 months. This figure was of 7 years for Teichmann¹⁷ and 4 years for Coe.¹¹ In agreement with the results of Giovanni,¹⁸ the median evolution was shorter among women. Hypertension and obesity were significantly correlated with a faster evolution to CRF.

There was no significant correlation found with calcemia, phosphatemia, calcium phosphate product, parathormone and hemoglobin. However alkaline phosphatases levels superior to 128 IU/L were correlated with faster evolution to CRF.

In agreement with Steven's results,¹⁹ urological treatment allowed the slackening of the evolution to CRF compared to the symptomatic treatment in our series. The end stage of renal insufficiency was reached after a median of 12 months in our patients. Singh and colleagues reported that 14 patients among 20 with nephrolithiasis evolved to ESRD in a time lower than one year.²⁰

Contrary to the age, gender and geographical origin which had no impact on the evolution to ESRD, obesity was significantly associated with a slower evolution. This result was also reported by Daniel.²¹ Secondary hyperparathyroidism and urological treatment were associated with slower evolution to ESRD. In the experience of Teichmann, all patients treated medically suffered a deterioration in their renal function against only 28% of surgically treated patients.¹⁷ The etiology of nephrolithiasis had no impact on the evolution to ESRD among our patients, nevertheless those having primary hyperoxaluria type 1 (PHA1) developed faster ESRD than those having a struvite or a primary hyperparathyroidism.

All our patients were treated by hemodialysis during a median evolution of 60 months. Sixteen patients died because of cardiovascular and infectious complications. The patient's survival rate at 1, 2, 3 and 5 years was respectively 97.6%, 95%, 92.8% and 69%, which was comparable with the survival rate of the totality of dialyzed patients.

No data concerning patient's survival was found in the literature. The age, gender and geographical origin had no impact on the patient's survival rate. O'Connor and colleagues showed that advanced age is a risk factor of renal function deterioration and mortality among patients having nephrolithiasis related ESRD.²² Hypertension had no impact on the patient's survival rate, whereas cardiopathy was associated with lower rate at 5 years.

Contrary to the results of Daniel²¹ we did not find any statistical correlation between the BMI and the patient survival rate. The nephrolithiasis etiology also had no impact on patient survival.

The fast evolution to ESRD (≤ 31.5 months) was significantly associated with a better survival compared to the slow evolution (> 31.5 months). The evolution to CRF can be prevented with an early etiologic diagnosis of nephrolithiasis and an appropriate treatment. However severe forms of renal stone disease are much less frequent than the common benign forms. This must be kept in mind in view of the disastrous consequences that may result from delayed or improper diagnosis and treatment.²³ In this regard, adequate analysis of stones and/or crystalluria together with proper metabolic evaluation are of crucial diagnostic value. They should never be neglected, especially in patients with the onset of nephrolithiasis in childhood, severely recurrent stones, nephrocalcinosis or incipient renal insufficiency as noted by Gambaro and colleagues.³ To this end the patient should be involved in the care of the nephrolithiasis.

The installation of medical software containing different clinical, biological and morphologic data accessible to all physicians from all specialties allows better coordination of the patient's care.

Conclusion

Nephrolithiasis remains the cause of potentially avoidable ESRD in too many patients despite recent major advances in the diagnosis and management of patients forming stones. These findings highlight the crucial importance of accurate stone analysis and metabolic evaluation to provide early diagnosis and proper therapy for a condition that may lead to ESRD through recurrent stone formation and/or crystal infiltration. ESRD and renal replacement therapy should be prevented in the future in most patients with renal stone disease.

Disclosure

The authors report no conflicts of interest in this work.

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