

LATERALITY OF SYMPTOMATIC CYSTINE CALCULI

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ABSTRACT

Objectives. To evaluate patterns of laterality in cystine stone formation to determine whether phenotypic expression of this genetic disease is distributed equally in each kidney. Cystinuria is a genetic defect that may result in the formation of recurrent cystine calculi. Significant nongenetic factors may play a role in the manifestation of this disease.

Methods. Thirty-four patients seen in the Stone Center at the University of California, San Francisco were retrospectively evaluated for treatments and patterns of symptomatic stone formation between 1989 and 2002. A conservative surgical regimen and routine radiographic examinations were used. Treatments were used as a surrogate for development of symptomatic calculi.

Results. The mean age at last follow-up was 38.2 years. The mean age at presentation was 18 years. The 34 patients underwent a total of 249 procedures, averaging 7.3 procedures per patient. Of the 34 patients, 29% required only unilateral surgery and formed unilateral symptomatic calculi exclusively ($P < 0.0001$) during their lifetime. Of the 10 patients with unilateral stone formation, 2 (20%) were female and 8 (80%) were male. Of the 24 patients with bilateral stone formation, 12 (50%) were female and 12 (50%) were male. Of the 10 patients with unilateral stone formation, 6 developed left-sided calculi and 4 developed right-sided calculi.

Conclusions. A subset of one third of patients with cystine stone formation will develop unilateral calculi exclusively during their lifetime. Understanding why the contralateral side did not form stones may provide insight into novel prophylactic regimens. The etiology of symptomatic unilateral cystine nephrolithiasis is unknown, but anatomic and external triggers should be considered. *UROLOGY* 62: 421–424, 2003. © 2003 Elsevier Inc.

Cystinuria is an autosomal recessive defect of the epithelial transport of cystine, ornithine, lysine, and arginine in the kidney and small bowel. Cystine calculi account for 1% to 2% of adult and 6% to 8% of pediatric urinary calculi.¹ Genetic expression and therapeutic utility in patients with cystinuria varies with subtype, as does the overall incidence of cystine stones.² Medical management of cystinuria involves reducing the concentration or increasing the solubility of urinary cystine. It is believed that 80% to 90% of cystine is reabsorbed in the proximal convoluted tubule of the kidney and that classic cystinuria (type I) is caused by a defect in the epithelial transport activator (primarily

from mutations in rBAT). Patients with non-type 1 cystinuria are believed to have mutations in the SLC7A9 gene, with the levels of cystinuria dependent on the particular mutation present.³ Phenotypic expression of cystinuria has been clearly demonstrated to have a basis in its genetic component⁴; however, the process and patterns of formation are less well identified. The differential expression of genetic mutations in each kidney of patients with cystinuria has not been demonstrated.

High stone-free rates can be achieved in patients with cystinuria without the need for open surgery using percutaneous nephrolithotomy⁵ and ureteroscopic stone retrieval.⁶ Chow and Strem⁷ noted a 73% 5-year stone recurrence rate and also found that the amount of quantitative urinary cystine, type of intervention required, and presence of residual calculi did not significantly affect the likelihood of stone recurrence.

Given what is known about cystinuria, one might expect that expression of this disease would follow a random distribution of expression in each

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TABLE I. Comparative demographics

Group	Total Patients (n)	Mean Age at Last Follow-up (yr)	Mean Age at Presentation (yr)	Mean Creatinine (mg/dL)	Right (%)	Left (%)	Male (%)	Female (%)
All patients	34	38 (37)	18 (16)	1.14			58.8	41.2
Unilateral stone formers	10	38 (33)	19 (13)	1.08	4 (40)	6 (60)	80	20
Bilateral stone formers	24	41 (38)	18 (16)	1.18			50	50

Numbers in parentheses are the median, unless otherwise noted.

kidney. Little statistical proof is available in published reports on the laterality of stone disease. Some evidence has shown that formation of calculi may be profoundly influenced by external and/or anatomic factors. Shekarriz *et al.*⁸ have argued that the laterality of stone formation may correlate with sleep posture and has postulated that this may relate to changes in renal blood flow. Anecdotally, many urologic surgeons believe that patients with recurrent stone formation may develop only unilateral calculi, although few data are available to prove this contention. It is assumed that cystinuria is a systemic disease with similar quantitative urinary cystine excretion from both kidneys. The phenomenon of unilateral cystine calculi would suggest that other significant factors are responsible for the development of stones. It has not been statistically confirmed in patients with cystinuria or other patients with recurrent stone formation. The presence of such a phenomenon would suggest that there may be important unexplained factors responsible for calculi formation in patients with cystinuria.

MATERIAL AND METHODS

PATIENT POPULATION

Thirty-four patients presented with symptomatic cystine calculi from 1989 to 2002 to a tertiary university-based setting (University of California, San Francisco). Additional interviews were conducted in 22 patients to obtain complete information. The data reported by patients was correlated with chart review.

TREATMENT PROTOCOL

All patients were offered medical prophylaxis with hyperdiuresis and alkalization as first-line therapy unless contraindicated, regardless of stone status. Thiols were offered as concomitant or second-line therapy followed by captopril. Surgery was performed only if patients with cystinuria presented with a symptomatic stone, a large stone that was growing, or significant or worsening hydronephrosis. Symptoms sufficient for treatment included recurrent urinary tract infection, severe pain, severe lower urinary tract symptoms, or persistent nausea and vomiting. Asymptomatic stones without hydronephrosis were observed and periodically imaged. Strat-

egies for treatment of calculi were identical for unilateral and patients with bilateral stone formation.

STATISTICAL ANALYSIS

Variables Evaluated. Procedures to treat calculi were used as a surrogate marker for the development of symptomatic calculi. Patients were also asked to recall the laterality of untreated calculi on the basis of their subjective experience of pain. All related treatments for a single stone episode were grouped together as one independent treatment unit for statistical analysis, because multiple procedures were often performed on a patient to treat a single stone episode. For example, if a complex staghorn calculus was treated with multiple interventions, these interventions would be considered one single treatment unit for analysis.

Statistical Modeling of Laterality of Calculi. We used the laterality of treatment of calculi as a surrogate for the development of calculi and analyzed the probability of developing recurrent stones only on one side. If stones requiring surgery are equally likely to occur on either side, the chance of developing unilateral stones in a particular patient must decrease with increasing numbers of independent surgeries. To test this null hypothesis, we created a test statistic equal to the total number of independent surgeries among patients with unilateral stone formation. We generated 10,000 simulated data sets with each patient's number of interventions to determine the likelihood of stones occurring only on one side following the null hypothesis assumptions. The proportion of the 10,000 simulated total numbers of surgeries among patients with unilateral stone formation that exceeded that observed in the actual data provided a *P* value for whether unilateral stones occur more frequently than expected by chance.

RESULTS

DEMOGRAPHICS

For all patients, the mean age at the time of last follow-up was 38.2 years (median 37.4, range 1 to 86). For patients with unilateral stone formation, the mean age was 37.8 years (median 33.3, range 1.3 to 86.2), and for patients with bilateral stone formation, the mean age was 40.7 years (median 38.4, range 17 to 81.8). The demographic information for the patients evaluated is summarized in Table I. Two patients (7%) presented with their first cystine calculi after the age of 50 years (70 and 53 years). The mean follow-up from initial stone presentation to the last follow-up visit was 26 years

(range 1 to 50) for all patients. The mean creatinine at the last follow-up was 1.1 mg/dL (range 0.6 to 1.6).

LATERALITY

During the course of their lives, the 34 patients averaged 7.3 procedures each and underwent a total of 249 procedures, including 92 (36.9%) percutaneous nephrolithotomies, 64 (25.7%) shock wave lithotripsies, 55 (22.1%) ureteroscopies, 32 (12.9%) open lithotomies, 4 (1.6%) nephrectomies, 1 (0.4%) cystolitholapaxy, and 1 (0.4%) percutaneous renal drainage. The 34 patients had 171 independent surgical treatment units. Of the 10 patients with unilateral stone formation, 6 (60%) developed only left-sided calculi and 4 (40%) developed only right-sided calculi as determined by an analysis of treatments, radiographic findings, and symptomatic history. All patients who reported and were confirmed to have undergone bilateral surgery also reported a history of bilateral pain; all patients who had only unilateral treatments reported only unilateral pain. Additionally, all patients who underwent unilateral surgery had only unilateral calculi by radiographic imaging.

Ten (29%) of 34 patients had stones requiring surgery on only one side (unilateral calculi), with the number of independent surgery units per patient ranging from 2 to 11; 85 of the total 249 procedures (33%) involved these patients. The 24 patients (71%) with bilateral surgery underwent 164 (67%) of the 249 total procedures, and the number of independent surgeries per patient ranged from 2 to 11.

The total number of independent surgical treatment units in the unilateral patients was 58 (for bilateral patients, it was 113) compared with an expected value of 15 under the null hypothesis. None of the 10,000 simulations produced a sum equaling or exceeding 58 ($P < 0.0001$); the maximal sum produced by the simulations was 44, giving strong statistical evidence that a subset of cystine patients form only unilateral calculi.

COMMENT

DEMOGRAPHICS

Patients with unilateral and patients with bilateral stone formation were comparable with respect to their age at initial presentation, length of follow-up, and renal outcome (serum creatinine). Our results confirm previously published data on the predisposition to form symptomatic cystine calculi during the first three decades of life.⁹ However, some patients presented with their first symptomatic cystine stone after the age of 30 years and even two after the age of 50 years. The factors inhibiting

stone formation in youth or triggering them later in life are unknown.

LATERALITY OF CALCULI

The known factors that influence the formation of cystine calculi include the genetic phenotype and hydration. One would expect that these factors would be expressed equally in each kidney. Shekarriz *et al.*⁸ suggested that discrepancies in renal blood flow may have an impact on the formation of unilateral calculi, although this hypothesis remains to be confirmed for patients with cystinuria.

Prior data have suggested a high rate of stone recurrence in patients with cystinuria, ranging from 0.84¹⁰ to 0.19¹¹ stone events per patient-year. Approximately 30% of cystinuric patients develop only unilateral calculi through the course of their life. Our data suggest that this was not by chance and was statistically significant ($P < 0.0001$). This was not secondary to a decreased number of interventions, because these patients had a proportionately greater number of symptomatic stones. Additionally, this was not secondary to residual calculi, because all interventions for residual calculi, for both unilateral and bilateral stones, were evaluated as one treatment unit. None of these patients had clear evidence of traditional anatomic risk factors for stone formation, such as ureteropelvic junction obstruction or vesicoureteral reflux.

These results suggest a possible intrinsic trigger for the development of symptomatic cystine calculi. Our data suggest that proportionately more men than women form unilateral calculi. The implications of this finding are unknown. Knowledge of what prevented the contralateral side from developing cystine calculi in patients who were predisposed to forming symptomatic calculi may minimize the morbidity of cystinuria and help elucidate inhibitors of stone formation.

In the past, it has been assumed that expression of quantitative urinary cystine excretion is equal bilaterally, but the expression of the transport defect may be unequal. An additional search for triggers and promoters of this transport defect and cystine stone formation is warranted. Possibilities include the importance of the postural effect of renal perfusion, microscopic anatomic differences in renal architecture, macroscopic differences not appreciated by computed tomography, and differential phenotypic expression in each kidney.

CONCLUSIONS

Most, but not all, symptomatic patients with cystinuria present early in life. Approximately one third of them develop exclusively unilateral calculi. Proportionately more men than women will develop unilateral cystine stones. The etiology of this phenomenon is unclear but suggests impor-

tant anatomic, intrinsic, and possibly physiologic factors that play a critical role in the phenotypic expression of this genetic disease.

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