STONE CLUSTERING OF PATIENTS WITH CYSTINE URINARY STONE FORMATION

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ABSTRACT

Objectives. To explore the history of symptomatic cystine stone formation. Cystinuria is a genetic defect that may result in the formation of recurrent cystine calculi.

Methods. Thirty-four patients with cystinuria were retrospectively evaluated for treatment patterns, medical prophylaxis, and renal outcome. Patients were offered a conservative surgical regimen and routine radiographic and laboratory follow-up and were encouraged to use medical prophylaxis. A Poisson regression model was used to analyze the patterns of stone formation.

Results. The mean age at presentation and at last follow-up was 18 and 38 years, respectively. Patients underwent a total of 249 procedures, with an average of 7.3 procedures per patient, including 37% percutaneous nephrolithotomies; 25.7% shock wave lithotripsy procedures; 22.1% ureteroscopies; 12.9% open lithotomies; and 1.6% nephrectomies. In 29% of patients, unilateral surgery only was required. With a conservative treatment regimen, no patient developed renal insufficiency or failure. The overdispersion estimated from the Poisson model was 5.03 ($P < 0.001$) if patients were evaluated from birth to last follow-up and 2.06 ($P < 0.001$) if followed from first presentation to last-follow-up, suggesting a clustering of stone events. Overdispersion was moderately related to increased age (older than 34 years).

Conclusions. The results of our study showed that patients with cystinuria develop symptomatic calculi in clusters, with a slight predominance of stone formation after the age of 34. The cause of the stone clustering is unclear. Renal function can be preserved with a conservative surgical treatment protocol. Contemporary medical prophylaxis may be ineffective. UROLOGY **63:** 630–635, 2004. © 2004 Elsevier Inc.

Cystinuria, a defect in the transport of dibasic amino acids, accounts for a small fraction of adult and pediatric calculi.[1] The incidence of cystinuria has been reported to vary from 1 in 2000 in England to 1 in 15,000 in the United States.[2] The disease expression and incidence of cystine calculi varies with the genetic subtype.[3]

Traditional medical prophylaxis has included hydration, dietary changes, and medications, including thiols, urinary alkalinization, glutamine, and captopril.[4]

The utility of medical therapy has been debated. Barbey *et al.*[5] argued that strict compliance with hyperdiuresis, alkalinization, and second-line treatment with thiols, may arrest the formation of new calculi. Chow and Streem[6] argued, however, that patients would continue to form cystine calculi despite compliance with medical prophylaxis. Medical treatment for patients with cystinuria can involve significant expense, discomfort, and inconvenience. Despite the possible benefits of medical therapy, patient compliance for long periods has been suboptimal. Recent data from the Duke University Medical Center has suggested that long-term compliance with medications is poor and that the durability of medical treatment for patients with cystinuria is limited.[7]

Data have suggested that cystinuria may adversely impact renal function despite medical treatment.[8] In a study of 95 patients with cystinuria, Assimos *et al.*[9] noted that patients with cystinuria had elevated creatinine levels (1.13 mg/dL) compared with matched patients with calcium oxalate stone formation (1.01 mg/dL). Although the lack of appropriate intervention may compromise renal function, aggressive surgical intervention may not be required to preserve renal function and

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may be accompanied by increased surgical morbidity. Chow and Streem[10] found that patients who underwent surgical intervention had a 5-year stone recurrence rate of 73% but quantitative urinary cystine, intervention type, and residual calculi did not affect the probability of stone recurrence. The factors that predict for cystine stone recurrence have not been definitively identified and little is known about the patterns of stone formation over long periods.

Anecdotally, our experience has been that many patients with cystine urolithiasis continue to develop symptomatic recurrent calculi requiring surgical intervention despite attempts at optimizing traditional medical prophylaxis. We observed that many patients required no intervention for prolonged periods but at other times multiple interventions were frequently needed. Our current study aimed to evaluate the patterns of stone formation, long-term compliance with medications, and outcome with surgically conservative treatment.

MATERIAL AND METHODS

Patient Population

Thirty-four patients presented with symptomatic cystine calculi from 1989 to 2002 to the University of California, San Francisco (UCSF) and were periodically evaluated in our stone clinic. Patients were asked to recall and confirm dates of procedures, spontaneous passage of calculi, and the type and frequency of medical prophylaxis. The information was verified by chart review. All patients provided written informed consent.

Treatment Protocol

Medical Treatment. All patients were offered medical prophylaxis with hyperdiuresis and alkalinization with bicarbonates or citrates as first-line therapy unless contraindicated. Thiols were offered as concomitant or second-line therapy, followed by captopril. Medical prophylaxis was offered to all patients with cystinuria, regardless of stone status. Serum creatinine levels were measured routinely every year and more frequently when clinically indicated. Twenty-four-hour urine samples were obtained to assess the severity of cystinuria and titrate the medical prophylaxis as needed.

Surgical Treatment. Patients with cystinuria and calculi were surgical candidates only if they presented with a symptomatic stone, a large stone that was growing, or significant or worsening hydronephrosis seen on imaging. Symptoms that would be sufficient for treatment included recurrent urinary tract infections, severe pain, severe lower urinary tract symptoms, and persistent nausea and vomiting. Asymptomatic stones without hydronephrosis were observed and periodically re-imaged. The large majority of stone treatments were performed at the UCSF. All treatments patients underwent during their lifetime, including those outside of the UCSF, were included for analysis.

Statistical Analysis

Variables Evaluated. Procedures to treat calculi were used as a surrogate marker for the development of symptomatic calculi. 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 sandwich therapy with percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy were given to a patient for treatment of a stone, this was analyzed as a single treatment unit. Repeated treatments of residual stones were counted as one intervention for analysis. Bilateral interventions offered at the same setting were analyzed as two independent treatment units.

Statistical Modeling. We assumed that the time from initial evaluation and the times of surgical interventions would be randomly distributed and follow exponential distributions if the risk of requiring surgery was constant over time. The number of surgical procedures, therefore, in a given period should follow a Poisson distribution. We modeled the number of surgical procedures in each calendar year by a Poisson regression model. Each full person-year of follow-up contributed one observation for these analyses. Overdispersion of interventions, or the degree of variability greater than what would be expected by chance, would result if a patient's procedures clustered within a calendar year. With clustering, counts would be more variable relative to the mean than expected from the Poisson distribution. To assess this, we estimated and tested overdispersion (over what would be expected by chance) by the Pearson goodness of fit chi-square test, correcting all other statistics for the overdispersion.

Additionally, we modeled longer term clustering in time by defining a predictor equal to 1 if the patient had had surgery in the previous year and otherwise equal to 0. If a disease tends to be more severe in particular age groups, this could cause clustering; therefore, we included age, broken into quartiles, to allow for a nonlinear effect, as a possible explanatory predictor. Clustering of interventions could also occur when patients were noncompliant with medication. We defined a predictor equal to 1 if the patient was taking medication during the year and 0 otherwise. Because counts from the same patient in different years may not be independent, even after including an effect for surgery in the previous year, we used the generalized estimating equation method to estimate and account for possible within-patient correlations. We performed analyses on full calendar years from birth to the end of follow-up and also from the first presentation to the end of follow-up. We used the Statistical Analysis System's Genmod procedure (version 8.2) to fit the Poisson models (SAS Institute, Cary, NC).

RESULTS

Demographics

The mean age at last follow-up was 38.2 years (range 1 to 86), and the mean age at presentation was 18 years; 5 patients presented with their first cystine calculi after age 30. Two patients (7%) presented with their first cystine calculi after age 50 (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). We evaluated 14 females and 20 males.

Laboratory Values

The most recent 24-hour urinalysis revealed a mean quantitative urinary cystine of 625 mg/day (median 526). The mean 24-hour urine values included pH 6.68 (range 5.82 to 7.5); volume 2.6 L (range 1.26 to 6.45); citrate 629 mg (range 325 to

TABLE I. ***Clustering effect of symptomatic calculi***

Period	Impact of Surgery in Previous Year	95% Lower Confidence Limit	95% Upper Confidence Limit	*P* Value
Birth to follow-up	5.03	3.27	7.74	<0.001
Presentation to follow-up	2.06	1.44	2.94	<0.001

Multiplicative effects on predicted number of surgeries in a calendar year, estimated from Poisson regression corrected for overdispersion and within-patient correlation. The impact is the ratio of the expected number of procedures in a given year if a patient required surgery in the prior year to the expected number if the patient did not require surgery in the prior year (no effect = 1).

TABLE II. ***Clustering effect relative to age***

	Group 1				Group 2			
Age by Year	Estimate*	95% Lower Confidence Limit	95% Upper Confidence Limit	*P* Value	Estimate†	95% Lower Confidence Limit	95% Upper Confidence Limit	*P* Value
0 to <10	0.10	0.04	0.26	<0.001	0.58	0.30	1.13	0.11
10–21	0.38	0.19	0.72	0.004	0.60	0.32	1.12	0.11
21–34	0.60	0.38	0.95	0.29	0.63	0.39	1.00	0.051
34–92	Reference age group							

* *Multiplicative effects on predicted number of procedures per calendar year, estimated from Poisson regression corrected for overdispersion and within-patient correlation, using years from birth to last follow-up.*

† *Multiplicative effects on predicted number of procedures per calendar year, estimated from Poisson regression corrected for overdispersion and within-patient correlation, using years since first presentation to last follow-up.*

1289); calcium 137 mg (range 48 to 251); uric acid 583 mg (range 419 to 1119); and oxalate 37 mg (range 12 to 68).

The mean creatinine at the last follow-up was 1.1 mg/dL (range 0.6 to 1.6). No patient required dialysis or renal transplantation. The analyzed stones were at least 80% cystine.

Treatment Patterns

Medical Treatment. Of 34 patients, 30 (88.2%) had taken medical prophylaxis at some time in their life. Long-term compliance was measured and included 19 (79%) of 24 patients compliant for citrate supplements, 13 (65%) of 20 for Thiola, 3 (21%) of 14 for penicillamine, 3 (33%) of 9 for bicarbonates, and 1 (33%) of 3 for captopril.

A model using years from first presentation to last follow-up estimated that patients averaged 2.4 times more surgical procedures when receiving than when not receiving medical treatment.

Surgical Treatment. Patients averaged 7.3 procedures and underwent a total of 249 interventions: 92 (36.9%) percutaneous nephrolithotomies; 64 (25.7%) shock wave lithotripsies; 55 (22.1%) ureteroscopies; 32 (12.9%) open lithotomies; 4 (1.6%) nephrectomies (performed prior to evaluation at UCSF); 1 cystolitholapaxy; and 1 percutaneous drainage. The 34 patients had 171 independent surgical treatment units.

Treatment Analysis

Tables I through III show the results of our Poisson modeling. Patients averaged 2.9 times more surgical procedures in the years following a year that required intervention than in the years with no prior intervention ($P < 0.001$). The estimated overdispersion for patients whose data were evaluated from birth was 5.03 ($P < 0.001$), indicating likely clustering within a year (normal = 1). The statistical significance was evaluated from the time of first presentation to the last follow-up visit with the overdispersion estimated to be 2.06 ($P < 0.001$).

To evaluate the cause of stone clustering, we assessed whether specific age categories were associated with clustering, in particular, age groups associated with extreme changes in hormonal levels (ie, puberty and menopause). As Table I indicates, younger men were at a decreased risk of developing clustering of their cystine calculi compared with men older than 34 years.

COMMENT

Renal Function

Our patients were treated conservatively, with surgical intervention reserved for those with symptomatic calculi, worsening hydronephrosis, or a large stone that was growing. Renal function was preserved with this scheme and, despite four prior nephrectomies, the mean creatinine was 1.1 mg/dL

TABLE III. *Clustering effect relative to hormonal levels*

	Group 1				Group 2			
Age by Hormones*	Estimate†	95% Lower Confidence Limit	95% Upper Confidence Limit	*P* Value	Estimate‡	95% Lower Confidence Limit	95% Upper Confidence Limit	*P* Value
Puberty†	0.73	0.45	1.18	0.20	0.58	0.37	0.89	<0.001
Declining hormones	1.34	0.88	2.04	0.17	1.04	0.68	1.57	0.87

* *Females: puberty = 12–25 yr; declining hormones = 46–55 yr; males: puberty = 13–25 yr; declining hormones = >55 yr.*
† *Multiplicative effects on predicted number of procedures per calendar year, estimated from Poisson regression corrected for overdispersion and within-patient correlation, using years from birth to last follow-up.*
‡ *Multiplicative effects on predicted number of procedures per calendar year, estimated from Poisson regression corrected for overdispersion and within-patient correlation, using years since first presentation to last follow-up.*

(range 0.6 to 1.6), consistent with the data presented by Assimos *et al.*[9] Despite the potential loss of renal parenchyma or nephrons, functionally, no patient required dialysis, renal transplantation, or developed chronic renal insufficiency. Our conservative treatment regimen adequately preserved renal function, and our data suggest that clinicians should use caution in treating asymptomatic patients with cystinuria. Symptomatic cystine stones appear to occur in clusters despite attempts at optimizing medical prophylaxis. Clustering did not appear to be related to medical prophylaxis.

Patterns of Stone Formation and Treatment

The utility of medical treatment has been debated in published reports. Our data did not address this question specifically, but we noted two interesting findings. First, a sizable number of patients were noncompliant with the medications despite rigorous counseling. Second, compliance with medications did not appear to prevent the development of symptomatic stones and did not decrease the need for surgical intervention. Patients required 2.4 times more treatment when compliant with medical prophylaxis than when not. This could be explained by an observation bias or greater patient compliance with prophylactic medications when the calculi were most symptomatic. At the minimum, however, it does suggest that patients do not form fewer symptomatic calculi while receiving medical prophylaxis.

Prior data have suggested a high rate of stone recurrence in patients with cystinuria. Chow and Streem[6] found 0.84 stone events per patient-year, but in a Japanese series, the rate was significantly lower at 0.19 stone events per patient-year.[11] Both of these studies evaluated patients for relatively short periods. The cause of this discrepancy is unknown; our data suggest stone clustering may have been responsible.

The likelihood of stone recurrence during a lifetime is high, probably secondary to periods of stone clustering. Conversely, our data demonstrated significant periods when patients with cystinuria did not form clinically relevant stones, regardless of the use of medical prophylaxis. The trigger for stone clustering did not appear to be noncompliance with medications, because patients formed more stones when compliant with medications. The trigger may be related to the hormonal levels of patients; older patients are at a greater risk of stone clustering than younger patients (Tables I to III). Injury to the urothelium or residual metal fragments from percutaneous ultrasound lithotripsy after surgery may trigger subsequent stone formation. This concept remains speculative, but it does not minimize our findings of stone clustering and our suggestion that surgical interventions should be minimized. More studies are required to determine the impact of surgery on the risk of cystine stone recurrence.

The clinician should recognize this phenomenon, because it may have a significant impact on patient care. If the onset of a clustering phase can be recognized, more frequent imaging and laboratory follow-up can minimize unnecessary morbidity. When patients are in quiescent asymptomatic periods, monitoring may be performed less frequently. We have found that the presence of asymptomatic, nonenlarging calculi does not necessitate surgical intervention and patients did well during prolonged treatment-free intervals.

Medical treatment may not mitigate the morbidity from stones or decrease the number of procedures required. Despite counseling, long-term compliance with medical therapy was suboptimal. Patients may have noted minimal benefit during the stone clustering periods, as they continued to form calculi despite cumbersome medical treatment. Conversely, quiescent periods were not perceived by patients to be associated with their medical compliance. In fact, during these periods, patients did well regardless of the use of medical prophylaxis.

We recognize the weaknesses in our study. In addition to the inherent flaws in any retrospective analysis, we could not reliably evaluate the likelihood of stone clustering relative to quantitative urinary cystine levels. Additionally, clustering may have occurred because of residual calculi. However, our analysis attempted to mitigate the impact this would have had by grouping all interventions for one stone as one event. It is possible that the clustering effect was secondary to an observation bias: increased clustering occurred secondary to patients being examined more frequently during particular periods. We do not believe this bias played a significant role in skewing our analysis, because our protocol primarily involved treating symptomatic calculi.

CONCLUSIONS

Most, but not all, symptomatic patients with cystinuria present early in life. Despite attempts at optimizing medical therapy, the need for intervention appears to occur in clusters, and, conversely, prolonged periods occur when patients remain asymptomatic. The initiators of clustering are unknown but appear to be partially age and possibly hormone related. Patients generally have poor long-term compliance with medications, but compliance increases during periods when procedures are required. Surgical treatment should be directed toward symptomatic relief. None of our patients developed renal failure during the conservative surgical treatment program. The medications appeared to have a minimal benefit during periods of stone clustering and may not be needed during quiescent periods.

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EDITORIAL COMMENT

The results of this large series of patients with cystinuria and long-term follow-up nicely corroborates the findings of prior reports that these patients require life-long surveillance and multiple urologic interventions, their stone disease recurs despite medical management, and that compliance with such regimens is poor. Most importantly, this article demonstrated that using a conservative surgical algorithm effectively preserves renal function over time. The authors reserved urologic intervention for symptomatic stones, documented stone growth, or significant or worsening hydronephrosis. All patients were provided with medical therapy and surveillance, including those with asymptomatic stable stone disease.

Another important point highlighted herein is that patients with cystinuria exhibit both periods of recurrent stones requiring intervention and quiescent periods without symptoms. However, this concept of "stone clustering" is not surprising, and the use of convoluted statistical analysis to demonstrate this was unnecessary. It seems unlikely that stone events would follow any distribution at all, particularly at a rate of one event per year. Although Chow and Streem[1] identified a rate of 0.84 stone events per patient-year, such events were defined as radiographic evidence of new stones or stone growth or spontaneous passage of a stone. The actual rate of intervention in that series was 0.32 per patient-year of follow-up and has been reported to be as low as 0.14 per patient-year in other series.[2] Furthermore, if interventions were grouped in the manner done in this article (albeit a valid point of methodology), the rate of interventions would be even less. Finally, extending the period of analysis back to the date of birth clearly skews all stones events to the right and offers no additional information.

As the authors suggest, clustering may indeed have been a result of the presence of residual calculi. Chow and Streem[3] showed that a stone-free result after endourologic intervention for cystine stones resulted in a longer median time to recurrence than those with residual calculi (1208 versus 346 days, respectively). As such, the presence of asymptomatic calculi profoundly affects the need for subsequent intervention. More-frequent imaging of this subset of patients may lead to earlier, less-invasive, and more-efficacious interventions.

Despite discouraging reports regarding the medical management of cystinuria, attempts at such therapy should not yet be abandoned. One certainly cannot make the proverbial horse drink. Nevertheless, a concerted effort between urologist, primary care physician, and patient, with routine 24-hour urinary cystine measurements, especially during quiescent periods, may provide enough impetus to sustain a lasting preventative regimen.

Advances in molecular medicine may allow for risk stratification based on the genetic identity and corresponding phenotype of each patient with cystinuria. In addition to the classic homozygous type I cystinuria linked to chromosome 2p21, an "intermediate" or "non-type I" phenotype associated with variable urinary cystine excretion and later-onset stone disease has been linked to chromosome 19q.[4] Additional investigation in this regard may contribute to a paradigm to predict the risk of stone recurrence and thereby guide surveillance and treatment.