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PROFILE OF THE BRUSHITE STONE FORMER

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Abstract

INTRODUCTION—The incidence of brushite stones has increased over the last 3 decades. We report our experience with brushite stone forming patients.

METHODS—From 1996 to 2008 we identified 82 patients with brushite urinary calculi. After institutional review board approval a review of our prospectively collected database was performed.

RESULTS—There were 54(65.9%) males and 28(34.1%) females. Mean age was 44 years (4–84). Prior stone events were reported by 69(84.1%) patients with 54(78.3%) having received shock wave lithotripsy (SWL). Bilateral calculi were present in 28(34.1%). Mean stone area was 29.2mm^2(2–130). Surgery was performed in 80 patients including: 63(76.8%) percutaneous nephrolithotomy (PCNL), 8(9.8 %) ureteroscopy, 3(3.7%) SWL, 6(7.3%) ureteroscopy and PCNL. After primary and secondary procedures seventy-six(92.7%) were rendered stone-free. Metabolic urine studies were available in 45 patients. All demonstrated one or more abnormalities: hypercalciuria 38(80.9%), urine pH > 6.2 in 29(61.7%), urine volume <2 L in 27(57.4%), hypocitraturia 22(46.8%), hyperuricosuria 8(17%), and hyperoxaluria 5(10.6%). Recurrent stone events occurred in 31(37.8 %) patients at a mean of 33(2–118) months from treatment.

CONCLUSION—Brushite stone formers are a treatment challenge. Almost a third will present with bilateral stones and stone burden is sizeable. Nearly 80% of patients report a prior SWL and recurrent stone events occurred approximately 3 years after treatment. All brushite patients in this cohort had an underlying metabolic abnormality, specifically brushite stones should be heralded as a marker for hypercalciuria. Based on these data we recommend all brushite stone formers undergo 24-hour urine studies and have close long-term follow-up.

Keywords

Brushite; nephrolithiasis; lithotripsy; calcium phosphate; percutaneous nephrolithotomy; hypercalciuria

Introduction

Urolithiasis is a common condition in the United States with an estimated prevalence of 11.7% by age 70 and is associated with considerable patient morbidity and occasional mortality.[1] The epidemiology of stone disease appears to be changing with an increase in the number of women and children diagnosed. Over the past 25 years the male to female ratio for the prevalence of renal calculi has decreased from 3:1 to currently less than 2:1.[2,3] Some

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have speculated this increase in affected females is due to changes in life-style factors, such as increasing obesity among women.[4] The increased diagnosis of urolithiasis in children has likewise been, in part, attributed to a rise in childhood obesity.[5,6]

Along with changes in the demographics of stone formers, a change in stone composition has also occurred. Approximately 15% of stone formers currently produce predominantly calcium phosphate stones (CaP). A quarter of CaP patients form stones containing brushite (i.e. calcium monohydrogen phosphate, $CaHPO_4 \cdot 2H_2O$).[7] Brushite is considered the precursor phase of hydroxyapatatite.[8,9] If brushite does not convert to hydroxyapatite, brushite stones will form. Unlike hydroxyapatite, brushite stones are hard making them difficult to remove and are particularly resistant to shock wave lithotripsy (SWL).[10] Parks and colleagues studied 1,201 patients and noted that the incidence of CaP calculi was increasing over the last 3 decades.[11] Mandel and colleagues further analyzed CaP stone formers and noted an increase in the prevalence of brushite stone disease.[12] Evidence also exists to support the theory that the occurrence of brushite stones is positively associated with SWL treatment.[11] Parks et al noted that CaP stone formers were more likely to have received SWL treatment than calcium oxalate stone formers independent of stone number or duration of stone disease. The authors also noted that patients with CaP stones were more likely to require surgical intervention than patients with calcium oxalate stones. Other authors have noted a decrease in stone-free rates after percutaneous nephrolithotomy (PCNL) in patients treated for CaP stones.[13]

Since brushite stone formers are encountered more frequently and have been shown to be difficult to treat they are likely to require more healthcare resources than calcium oxalate stone formers. Unfortunately, little is known about the profile of the brushite stone former. The goal of our study is to further characterize the brushite stone former by reviewing our prospectively collected brushite stone database.

Materials and Methods

After institutional review board approval, patients with brushite renal or ureteral calculi were enrolled in our prospectively collected database. From January 23, 1996 to February 11, 2008 we identified 82 brushite stone patients. To be considered for the database a patient must have a documented stone containing any amount of brushite on stone analysis. The percentage of brushite and secondary components for each retrieved stone was recorded. Demographic and surgical data for each patient was collected. Post surgical stone-free status was determined by non-contrast computed tomography CT scan for PCNL, and noncontrast CT or plain abdominal x-ray (KUB) for patients treated with ureteroscopy or SWL. Twenty-four hour urine metabolic studies were performed either preoperatively, or 4 to 6 weeks postoperatively with patients on an unrestricted diet.

Due to the referral nature of our practice not all patients were regularly followed by our practice postoperatively. For those patients continuing care with our practice, standard follow-up consisted of a 6 week postoperative evaluation and then yearly evaluations thereafter. If abnormalities were noted on 24-hour urine metabolic studies then the studies were repeated every 3 months while dietary and medication changes were made until the metabolic profile stabilized, at which point 24-hour urine studies were then performed yearly with a KUB and urinalysis. If the patient did not appear to have metabolically active stone disease then follow-up appointments were decreased to yearly with a KUB and urinalysis. Stone recurrence episodes were considered significant if a stone was passed spontaneously with specimen available for analysis or an obvious stone was identified on imaging that was subsequently passed, or treated with surgical intervention.

Results

The mean age of the 82 brushite patients identified was 44 years (range 4 to 84), with 54 (65.9%) males and 28 (34.1%) females. At the time of capture in our database 69 (84.1%) patients reported a prior stone event, of which 54 (78.3%) were treated with previous SWL. Table 1 provides details of the 989 prior stone treatments. Twenty-two (26.8%) of the patients had a positive family history for stone disease, with a first degree relative with symptomatic stone disease. Mean stone area at presentation was 29.2 mm^2 (range 2 to 130). There were 35 (42.7%) left sided stones, 19 (23.2%) right sided, and 28 (34.1%) bilateral. Of the patients with a history of stone disease prior to presentation the mean time from their previous stone to the presenting stone was 21.1 months (range 1 to 96).

Except for the 2 (2.4%) patients that spontaneously passed their presenting stone, all patients required surgical intervention for symptomatic stone disease, which includes hematuria, pain, or infection. Surgical intervention included: PCNL 63 (67.8%), ureteroscopy 8 (9.8%), SWL 3 (3.7%), and combination ureteroscopy and PCNL 6 (7.3%). After all primary and secondary surgical interventions 76 (92.7%) of the patients were rendered stone-free. Figure 1 is a KUB from a patient requiring both a primary and secondary PCNL to be rendered stone-free. Of the 63 PCNL procedures, 23 (36.5%) required a secondary PCNL to achieve stone-free status.

Stone composition was available for all patients in the cohort. Pure brushite stones were present in 64 (78.4%) patients. Brushite mixed with hydroxyapatite was noted in 6 (7.3%) and mixed with calcium oxalate in 5 (6.1%). There were 7 (8.5%) patients who presented with non-brushite stones (all calcium oxalate mixed with apatite), but had a documented history of brushite stones. Of the entire cohort, 16 (19.5%) patients had a history of a prior non-brushite stone, but subsequently converted to brushite calculi at time of enrollment in the database.

There were 53 patients (65.9%) who had follow-up of at least 1 month. Of these 53 patients mean follow-up was 4.1 years (range 1 month to 12.5 years). Recurrent stone disease requiring surgical intervention occurred in 31 (58.5%) patients at a mean of 32.9 months (2 to 118 months) from date of our initial treatment. Twenty-four hour urine studies were available for 45 patients in the database (Table 2). A total of 112 studies were available for analysis. All patients demonstrated one or more abnormalities with hypercalciuria 38 (80.9%) and elevated urine pH greater than 6.2 in 29 (61.7%) being the most common findings. Of the patients with follow-up the following medications were instituted for their stone disease, most patients received more than one medication: thiazide diuretics 32 patients, potassium citrate therapy 17, potassium supplementation 9, allopurinol 8, amiloride 1, ammonium chloride 1.

Discussion

In the majority of kidney stones calcium oxalate is the main constituent and CaP is present in amounts ranging from 1% to 10%.[14] When the CaP constituent becomes the majority of the stone composition present then the stone is considered a CaP stone. In general, CaP is present in one of three forms in the urinary tract: hydroxyapatite, calcium carbonate phosphate, and brushite. Of the urinary forms of CaP brushite is the most problematic. Brushite is one of the few forms of urinary calculi that are resistant to SWL,[10] along with cystine and some calcium oxalate monohydrate stones. In a study comparing brushite to idiopathic calcium oxalate stone formers, after adjustments were made for sex, numbers of stones, and duration of stone disease, brushite stone formers require a greater number of SWL treatments.[11] Furthermore, a recent study has indicated that stone-free rates after

PCNL are decreased in patients with CaP stones.[13] Thus, one can assume that brushite stone patients may require multiple secondary SWL, ureteroscopic, or PCNL treatments to be rendered stone-free. Papillary biopsies of stone forming patient at time of PCNL indicate that brushite stones develop in the presence of a distinctive crystal-associated nephropathy.[15] In the presence of documented nephropathy small cohort studies demonstrate that brushite stone formers have a higher serum creatinine and lower 24-hour urine creatinine clearance than other stone formers;[15] however, large cohort studies have not identified an increase in the risk of renal insufficiency in patients with brushite stones.[11] To date, what causes the persistence of the brushite crystal phase with development of overt stones rather than conversion to hydroxyapatite is not yet understood.

There is evidence to support that brushite stone formers are increasing in incidence and are more commonly encountered by urologists. Parks and colleagues found that the calcium phosphate fraction in stones had increased over the last 3 decades, along with an increase in urinary pH and brushite saturation.[11] Mandel and colleagues studied 33,198 stones from the National Veterans Administration Crystal Identification Center in 2002.[12] Compared to a 1989 survey of crystal study, the percentage occurrence of hydroxyapatite stones had increased 1% (26.9% to 27.9%) and brushite stones had increased 3% (1.7% to 4.14%). The authors further noted that some patients who once produced calcium oxalate stones had converted to CaP stone producers over time.

Similar to Mandel's observations, we noted that a significant number of patients, 17% of our cohort, had converted from another stone composition to brushite stones. We also noted more men than women affected with brushite stones similar to what has been classically observed for calcium oxalate stone disease. Prior stone events were reported by 84% of patients and nearly 80% having received a prior SWL treatment. Stone size was in general large, with a mean stone surface areas of nearly 3 cm^2; however, utilizing primary and secondary surgical procedures stone-free rates were over 90%. All patients with 24-hour urine studies had a noted abnormality, with hypercalciuria being the most common in 80% of patients followed by elevated urine pH. Compared to the 5–10% rate of hypercalciuria in the general population[16] and 30–60% rate found in idiopathic stone formers, the rate of hypercalciuria in our brushite cohort is much higher. Parks and colleagues have also noted a higher rate of hypercalciuria in patients who develop brushite stones compared to idiopathic calcium oxalate controls.[17] In our cohort stone recurrences were common at a mean of 3 years post surgical intervention.

Previous studies have indicated that women are more likely than men to form CaP stones.[11,18] However, like Parks and colleagues[11] we noted that when CaP stones were divided into individual subtypes brushite stone composition was strongly associated with male gender. These findings lead us to question what role hormones and/or genetics play in the conversion of brushite to hydroxyapatite.

Unlike recent surgical series where stone-free rates in patients with CaP stones were decreased after PCNL (stone-free rates from 66% to 71%),[13] in our series final stone-free rates were high at nearly 93%. However, it should be noted that over a third of patients in our cohort required a secondary PCNL procedure to attain such high stone-free results. Despite achieving near complete stone-clearance in our cohort of brushite patients, there was still an almost 60% stone recurrence rate at a mean of 3 years from date of surgery. This rate of long-term recurrent disease is higher than what has been observed for the general population after SWL (54%) and PCNL (37%),[19] further indicating the severity of stone disease in the brushite stone former. Of note, despite the high recurrence rates, with aggressive surgical intervention and strict metabolic evaluations we were able to prolong time to stone recurrence from a mean of 21 months preoperatively to 33 months after our interventions.

Although Pak and colleagues have previously reported an association between the amount of CaP composition in a stone and metabolic abnormalities, such as renal tubular acidosis and primary hyperparathyroidism,[20] we found no such association in our brushite cohort. No patient in this cohort had a systemic acidosis and, therefore, none had complete RTA. Many of these patients had low citrate and elevated urine pH and could be viewed as having a form of incomplete RTA. In fact, in our cohort nearly all the patients were found to have hypercalciuria, and most had elevated urinary pH leading us to conclude that brushite stone disease should be considered a harbinger for hypercalciuria. Based on the metabolic study results and high stone recurrence rate observed in our cohort, we recommend that all patients with brushite renal or ureteral calculi undergo a metabolic stone evaluation and have close long-term urologic follow-up. Since brushite stone disease appears to be increasing we conclude that these patients will become a more common patient seen by urologists.

The cause for the observed increase in brushite stone disease is not yet understood; however speculations of possible mechanisms have been made. Evan and colleagues studied papillary biopsy taken from brushite stone formers undergoing PCNL.[15] They noted hydroxyapatite plugs filling the lumens of the terminal collecting ducts with surrounding epithelial damage and destruction. Furthermore the interstitium around the affected tubules were scarred and inflamed. The authors noted that brushite stone formers in their cohort had received a greater number of prior SWL treatments compared to calcium oxalate stone formers. Evan et al theorize that SWL could produce the renal damage and subsequent brushite stone formation in some patients. They further suggest that the current liberal use of citrate therapy without attention to urinary pH may result in the rising prevalence of CaP stones over the last 3 decades by increasing CaP supersaturation. In our study nearly all of the patients had received a prior SWL similar to that observed by Evan et al.; however, it is uncertain if the high number of prior SWL in our brushite patients is just a result of our practice being a tertiary referral center or an underlying cause of the brushite stones. Furthermore, unlike Evan and colleagues we could find no obvious associate between citrate usage and brushite stone disease.

Certain limitations of the study must be recognized. First, due to the referral nature of our practice not all patients were followed at our clinic; and thus some patients were lost to follow-up. Second, although the database was prospectively collected, the data was retrospectively reviewed, which can introduce collection bias. Finally, there is no control group to compare with the brushite stone formers. Despite these limitations the current study represents the largest study to focus on brushite stone formers, allowing us to characterize a difficult treatment cohort.

Conclusion

Although we do not yet know the cause for brushite stone formation nor do we fully understand why the incidence of brushite stone disease is increasing, we now can characterize the brushite stone patient profile. We found that brushite stone formers are more likely to be male and that stone burden is sizable. Stone recurrence is common with nearly 80% of patients report a prior SWL. Brushite stone patients can have a high success rate with surgical intervention, but secondary procedures may be necessary. After institution of definitive therapy recurrent stone events were still common, but prolonged compared to pretreatment. All brushite patients in this cohort had an underlying metabolic abnormality, specifically the presence of brushite stones should be considered a marker for hypercalciuria. Based on these data we recommend all brushite stone formers undergo 24-hour urine metabolic evaluations and receive long-term follow-up for their stone disease.

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Figure 1.

Table 1

List of stone events for the 69 brushite stone patients reporting a history of stone at time of presentation.

	N=989	%
Spontaneous Passage	332	33.6
Shock Wave Lithotripsy	322	32.6
Left	182	
Right	140	
Ureteroscopy	218	22.0
Left	107	
Right	111	
Percutaneous Nephrolithotomy	94	9.5
Left	46	
Right	48	
Open Lithotomy	22	2.2
Nephrectomy	1	0.1

Table 2

Twenty-four hour urine values and abnormalities for 45 patients with brushite stones. All patients demonstrated at least one metabolic abnormality.

Variable	Mean	Range
Volume **(L)**	1.87	0.24–3.75
pH	6.4	5.2–7.9
Citrate **(mg/spec)**	493.5	21–1724
Calcium **(mg/spec)**	319.2	72–847
Oxalate **(mg/spec)**	37.8	5.3–88
Uric Acid **(mg/spec)**	24.01	0.12–760
Sodium **(mmol/spec)**	195	5–512
Weight (Kg)	83.2	53.6–136