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Surgical Management of Stone Disease in Patient with Primary Hyperoxaluria

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Abstract

Objectives—To present our experience with surgical management of nephrolithiasis in patients with primary hyperoxaluria (PH).

Methods—A retrospective chart review from 1994–2012 was performed to identify patients with diagnosis of PH.

Results—A total of 14 patients with PH were identified with median follow-up of 18.6 years (range: 0.9–51). Median age at initial symptom and subsequent diagnosis were 6.7 years (range: 1.1–35.5) and 0.42 years (range: 0–33.25), respectively. Patients underwent a total of 54 procedures at our institution including: ureteroscopy 27 (50%), percutaneous nephrolithotomy 15 (28%), shock wave lithotripsy 8 (15%), and combined procedures 4 (7%). Overall non-intraparenchymal stone free rate after first, second, and third procedure(s) were 59%, 76%, and 78%, respectively. On average 1.6 procedures (range: 1–4) were required to rid patients of symptomatic stones, which subsequently afforded them a mean of 3.62 years (range: 0.25–21.5) without the need of additional intervention. There were 6 Clavien grade III complications in 4 patients, including immediate postoperative ESRD in 3.

Conclusions—Despite optimal medical and surgical management, patients experience recurrent acute stone events requiring multiple urologic interventions. Significant complications such as ESRD can occur secondary to surgical intervention.

Keywords

primary hyperoxaluria; oxalosis; nephrolithiasis; nephrocalcinosis

Introduction

Primary hyperoxaluria (PH) is a rare autosomal recessive disease caused by specific hepatic enzyme deficiencies that influence glyoxylate metabolism. Three different forms of PH (type 1, 2, and 3) with varying degrees of disease severity have been described, and other types have been suggested without a confirmed etiology.^{1–4} PH is characterized by

endogenous overproduction of oxalate by the liver resulting in hyperoxaluria. Calcium oxalate stones and nephrocalcinosis are the principal manifestations of PH leading to chronic kidney disease (CKD) and end-stage renal disease (ESRD) if untreated. If PH progresses, liver and kidney transplantation may be needed to correct the underlying endogenous overproduction of oxalate and replace lost kidney function.⁵

While increase fluid intake combined with inhibitors of calcium oxalate crystallization (citrate or neutral phosphate administered orally) are the corner stone for management, medical intervention does not treat previously formed stones nor fully prevents recurrent nephrolithiasis.^{3, 6–8} Pyridoxine when given at pharmacologic doses is beneficial in a subset of patients with PH type 1, but does not benefit the majority of PH patients. Thus, patients with PH often develop nephrolithiasis and require multiple urologic procedures during their lifetime for management of these. The rarity of the disease creates a lack in data and guidance on the urologic management of nephrolithiasis in the PH patient population. In addition, as a result of inflammation and parenchymal calcification that occurs with PH,⁹ rendering such patients stone free can be difficult through an endoscopic approach. As a tertiary referral center for PH, we here report our experience with urologic surgical interventions for management of nephrolithiasis in patients with PH at our institution.

Methods

After institutional review board approval the Mayo Clinic electronic medical records from 1994 to 2012 were queried to identify patients who have been evaluated at Mayo Clinic for management of PH. Data on age, gender, presentation, type of PH, type of procedure, post procedure complications, stone composition, pre and post procedure glomerular filtration rate (GFR), and follow-up were retrospectively reviewed. The patient registry from the Mayo Clinic Primary Hyperoxaluria Center, part of the Rare Kidney Stone Consortium (www.rarekidneystones.org), was utilized to cross reference and verify demographic data obtain from chart review. Given that nephrocalcinosis, in the form of urothelial and parenchymal calcifications commonly found in PH kidneys, makes it difficult to determine if patients are radiographically stone-free, we defined successful treatment as complete clearance of non-intraparenchymal stones (i.e. free floating intraluminal stones) per targeted renal unit. Each renal unit constituted of the ureter, renal pelvis, and calyces. Pre-operative and postoperative GFR were estimated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation¹⁰ to determine CKD stage prior to any procedure or acute stone event, and assess if the patient's CKD stage remained stable, progressed, or improved after procedure. Fisher's exact test was used for statistical analysis to compare success rate among endoscopic modalities.

Results

A total of 149 patients with median follow-up of 11.6 years (range: 0–51) evaluated at our institution for PH were identified (Table 1). Diagnosis was made before the age of 18 year in 65%, with the remainder diagnosed as adults. Distribution of PH subtype was 77% type 1, 11% type 2, 10% type 3, and 2% unclassified. Median age at initial symptom and subsequent diagnosis were 5.6 years (range: 0.1–53) and 10.9 (range: 0–74) years,

respectively; with an overall median delay in diagnosis of 2.7 years (range: 0–62). Presenting symptoms included flank pain due to stone in 52% and hematuria in 31%. Nephrocalcinosis was present on radiographic imaging at time of diagnosis in 24% of patients. A total of 28 (19%) patients presented with ESRD; furthermore, ESRD developed in 34 (28%) patients at a median time from diagnosis of 15.4 (range: 0.1–51) years. Pyridoxine therapy response for type 1 PH was 31 (27%) partial, 14 (12%) complete, 12 (11%) none, and 57 (50%) unknown. A total of 362 urologic procedures for treatment of nephrolithiasis (Table 2) were reported in 67 (45%) patients, with an average of 5 (range: 1–29) procedures per patient. Procedures included shock-wave lithotripsy (SWL) in 148 (41%), ureteroscopy (URS) in 98 (27%), percutaneous nephrolithotomy (PCNL) in 64 (17%), cystoscopy 21 (6%), open nephrolithotomy (ONL) in 14 (4%), and unknown in 17 (5%).

A total of 14 patients with median follow-up of 18.6 (range: 0.9–51) years underwent urologic procedures for the treatment of nephrolithiasis at our institution. Median age at initial symptom and subsequent diagnosis for this subset of patients were 6.7 years (range: 1.1–35.5) and 0.42 years (range: 0–33.25), respectively. Median stone size was 1.6 cm (range: 0.5–4.5 cm). PH subtype was 86% type 1, 7% type 2, 7% type 3. All patients were on medical therapy for stone prevention during follow-up and pyridoxine response for type 1 PH was partial in 8 (67%), complete in 2 (17%), none or unknown in 2 (16%). A total of 54 urologic procedures were performed in these 14 patients and included: 27 URS, 15 PCNL, 8 SWL, and 4 combined procedures (Table 3). There were 23 primary URS (43%) in 11 patients, with a stone-free rate of 57%. A secondary URS for the same stone was performed in 3 cases (13%) with a final stone free rate of 65%. A primary URS followed by a secondary PCNL was performed in 2 patients and a tertiary PCNL was necessary in 1 patient. There were 10 primary PCNL (19%) procedures in 7 patients, with a stone-free rate after the primary PCNL of 70%. A secondary PCNL for the same stone episode was performed in 2 cases (20%) with a final stone free rate of 90%. Overall non-intraparenchymal stone-free rate for endoscopic procedures (URS and PCNL) after first, second, and third procedure were 59%, 76%, and 78%, respectively. Post procedure GFR remained stable in 71%, improved in 13%, worsen in 8%, and was unknown in 8% of 38 endoscopically managed cases. There were 8 SWL procedures in 5 patients for treatment of acutely obstructing stones. Intraoperative observation reported “excellent stone fragmentation” for all cases. Postoperative imaging demonstrated 50% reduction in stone burden in 5 cases (63%). Ancillary procedure post SWL were required in 2 (40%) patients and included URS. A planned sequential procedure after SWL was performed in 2 patients and included URS and PCNL, and URS and SWL. On average 1.6 procedures (range: 1–4) were required to rid patients of symptomatic stones, which subsequently afforded them a mean of 3.62 years (range: 0.25–21.5) without the need of additional intervention. Acute stone events (including reported spontaneous stone passage) occurred at a rate of once every 2.83 (range: 0–21.5) years. Stone compositions for 45 stones were available for analysis. Calcium oxalate monohydrate was the predominant constituent in 44/45 stones (Twenty of these were 100% calcium oxalate monohydrate), 22 contained a fraction (between 5–40%) of calcium oxalate dihydrate, one stone contained a fraction of calcium phosphate (10%), and one stone was mostly calcium phosphate (70%).

A total of 6 complications (Clavien grade III) were observed in 4 patients who underwent endoscopic procedure. A chest tube for the management of a pleural effusion after PCNL was required in 1 patient. Retrograde stent placement for pain after PCNL was required in 1 patient, and this patient also required ICU admission for aspiration pneumonitis at time of this procedure. Three patients developed ESRD within 30 days of procedure. Two of them with preexistent stage 3 CKD at age 20 and 13 developed ESRD after presenting with acutely obstructing stones and superimposed acute kidney injury with GFR under 33 mL/m/1.73 m² at the time of the stone removal procedure. Time between acute stone event and intervention was more than 12 hours. A third patient with stage 3 CKD, age 67, unexplainably progressed after he was dismissed from hospital with improved GFR. Each of these patients had type 1 PH and went on to receive combined liver and kidney transplants.

Discussion

Primary hyperoxaluria is a rare inherited disease with variable age of symptom onset and diagnosis. True prevalence is unknown, but it has been estimated based on surveys of urologist and nephrologist to be 1 to 3 cases per 1 million persons with an incidence rate of approximately 1 case per 120,000 live births in central Europe.^{3, 11–14} ESRD occurs in 1 to 2% of cases of pediatric PH patients and in over 50% of adults diagnosed with PH.^{15, 16} It is well established that patients with recurrent nephrolithiasis are at increased risk for CKD, and this risk is attributed to repeat bouts of infection, obstruction, inflammation from interstitial crystal deposition, and progressive nephrocalcinosis in certain conditions.^{17, 18} However, patients with PH are at a substantially greater risk of ESRD due to severe intraparenchymal calcifications, inflammation, and scarring as well as multiple recurrent symptomatic stone episodes.

In our study, we found that only 22 (59%) of the primary endoscopic procedures were successful at removing the symptomatic stone burden and 9 additional procedures were required for a targeted stone-free rate of 76% after secondary and 78% after tertiary procedures. PCNL was the most successful at rendering patients clear of their symptomatic stone burden with a 70% primary and 90% secondary success rate. URS render patients clear of their symptomatic stone burden with a 57% primary and 65% secondary success rate. In our cohort, PCNL had higher stone-free rate than URS (90% vs. 65%) although this was not statistically significant. It is worth noting that in six patients treated with URS, only the obstructing stone was treated and there was no attempt to clear non-obstructive stones. These six patients were noted to have small non-obstructive stones which could have been easily cleared and potentially increase the URS stone-free rate to 76%. In the last five years, we have managed non-obstructing stones more aggressively via URS. Of twelve URS performed after 2009, 92% of renal units were rendered free of non-intraparenchymal stones.

While PCNL has excellent stone-free rate, it is more invasive, associated with more complications, and longer hospital stay.¹⁹ Before performing PCNL, one must consider that PH patients may have large amount of nephrocalcinosis which can make stone burden look larger than what it truly is (Figure 1). We recommend that if nephrocalcinosis makes estimating stone burden difficult, an initial URS be performed to assess the true burden of

stones within the collecting system. If a large amount of stone burden is confirmed within the collecting system then the procedure can be converted to PCNL under the same surgical anesthetic.

Shock-wave lithotripsy is an effective treatment for adults and children with stone-free rates ranging between 58 to 83%.^{20, 21} Al-abadi et al recently evaluated the success of SWL in treating 23 stones in 10 patients with PH.²² Successful treatment was defined as 50% reduction in stone burden or complete resolution. In their cohort, SWL was effective in 43% of stones (10 patients), and repeat SWL was required in 61% of patients. These results were similar to the Tunisian cohort in which seven patients with PH underwent SWL and only three (43%) were successful.²³ In our cohort, 5 patients underwent SWL for treatment of 8 stones. Five targeted stones (63%) were treated successfully using same definition of success, while 2 patients required URS for treatment of steinstrasse. A number of issues regarding SWL should be considered in patients with PH. Calcium oxalate represents the most common stone in PH, and this stone composition can in some circumstances be resistant to fragmentation.^{22, 24} Nephrocalcinosis makes preoperative imaging difficult to interpret in patients with PH, which can lead to unnecessary shock-waves deliver to the kidney.^{22, 25} Although it is difficult to extrapolate the observed side effects of shock-waves energy in animal studies, one cannot ignore the risk of parenchymal damage, particularly in small kidneys.²⁶ Additionally, there are reports of patient with PH developing progressive renal failure after SWL.^{18, 27, 28} Thus, based on our experience with SWL, we rarely perform SWL in patients with PH.

Another point noted within the study was that all of our patients were on medical therapy for stone prevention, yet they continue to form stones requiring surgical intervention. Therefore, we believe that preemptive management of nephrolithiasis may have a beneficial impact on their risk for progressive kidney disease by avoid invasive procedures required for large stone burden.^{17, 22} Our complication rate (Clavien III) was 11% with all but one occurring after a PCNL, which is similar to the 15% reported in the literature.²⁹ Three patients developed ESRD within 30 days of procedure. Two of the patients developed ESRD after presenting with acutely obstructing stones and GFR under 33 mL/m/1.73 m². When the GFR drops to 30 to 45 mL/m/1.73 m² of body-surface area in patients with PH, the kidneys are no longer able to effectively excrete the excess oxalate which leads to systemic oxalosis.³⁰ Any deterioration in renal function can impact the narrow equilibrium between the production and excretion of oxalate resulting in an oxalosis crisis. Due to this fine balance of oxalate homeostasis, it has been our practice in recent years to admit any surgical PH patients preoperatively for intravenous fluid hydration to avoid dehydration that may result in a change in GFR and subsequent precipitation of oxalate. Most patients are kept overnight for continued intravenous hydration post procedure, even if the procedure is a simple URS. One can make the argument that any acutely obstructing stone in a PH patient should be treated emergently in order to restore renal function, maintain oxalate equilibrium, and prevent oxalosis crisis.

This study has its limitations that must be acknowledged including retrospective design, lack of uniform follow-up, and change in surgical philosophy and technique over the study time period. However, this review represents one of the largest reports on the endoscopic

management of nephrolithiasis in patients with PH with long follow-up. With a large cohort of PH patients we are able to identify certain difficulties such as oxalosis crisis and confounding nephrocalcinosis which can compromise surgical outcomes; thus providing valuable data to the practicing urologist.

Conclusion

Primary hyperoxaluria is a rare heterogeneous disease with variable age of symptom onset, age at diagnosis, and clinical course. Early screening is warranted in patients with recurrent or early age calcium oxalate nephrolithiasis, as delay in diagnosis is common. Despite optimal medical management, many patients will develop recurrent nephrolithiasis requiring multiple urologic procedures to render them stone-free. Nephrocalcinosis makes interpretation of preoperative imaging and rendering patients radiographically stone-free difficult. Since patients are at high risk of prompt stone re-growth of residual fragments, stone-free state is best achieved by stone removal by direct visualization. Finally, it must be recognized that subtle changes in GFR in patients with PH can result in oxalosis crisis and has the potential for the development of ESRD. Therefore any acute stone event should be treated aggressively in order to prevent oxalosis crisis.

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References

1. Purdue PE, Lumb MJ, Fox M, et al. Characterization and chromosomal mapping of a genomic clone encoding human alanine:glyoxylate aminotransferase. *Genomics*. 1991; 10:34. [PubMed: 2045108]
2. Cramer SD, Ferree PM, Lin K, et al. The gene encoding hydroxypyruvate reductase (GRHPR) is mutated in patients with primary hyperoxaluria type II. *Human molecular genetics*. 1999; 8:2063. [PubMed: 10484776]
3. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. *Kidney international*. 2009; 75:1264. [PubMed: 19225556]
4. Belostotsky R, Seboun E, Idelson GH, et al. Mutations in DHDPSL are responsible for primary hyperoxaluria type III. *American journal of human genetics*. 2010; 87:392. [PubMed: 20797690]
5. Bergstralh EJ, Monico CG, Lieske JC, et al. Transplantation outcomes in primary hyperoxaluria. *American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2010; 10:2493.
6. Cochat P, Hulton SA, Acquaviva C, et al. Primary hyperoxaluria Type 1: indications for screening and guidance for diagnosis and treatment. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association*. 2012; 27:1729.
7. Leumann E, Hoppe B, Neuhaus T. Management of primary hyperoxaluria: efficacy of oral citrate administration. *Pediatric nephrology*. 1993; 7:207. [PubMed: 8476722]
8. Milliner DS, Eickholt JT, Bergstralh EJ, et al. Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. *The New England journal of medicine*. 1994; 331:1553. [PubMed: 7969325]
9. Worcester EM, Evan AP, Coe FL, et al. A test of the hypothesis that oxalate secretion produces proximal tubule crystallization in primary hyperoxaluria type I. *American journal of physiology. Renal physiology*. 2013; 305:F1574. [PubMed: 24089413]
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Annals of internal medicine*. 2009; 150:604. [PubMed: 19414839]

11. Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. *Pediatric nephrology*. 2003; 18:986. [PubMed: 12920626]
12. Cochat P, Liutkus A, Fargue S, et al. Primary hyperoxaluria type 1: still challenging! *Pediatric nephrology*. 2006; 21:1075. [PubMed: 16810517]
13. van Woerden CS, Groothoff JW, Wanders RJ, et al. Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association*. 2003; 18:273.
14. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association*. 1995; 10:2224.
15. Harambat J, van Stralen KJ, Espinosa L, et al. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. *Clinical journal of the American Society of Nephrology: CJASN*. 2012; 7:458. [PubMed: 22223608]
16. van der Hoeven SM, van Woerden CS, Groothoff JW. Primary hyperoxaluria type 1, a too often missed diagnosis and potentially treatable cause of end-stage renal disease in adults: results of the Dutch cohort. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association*. 2012; 27:3855.
17. Rule AD, Krambeck AE, Lieske JC. Chronic kidney disease in kidney stone formers. *Clinical journal of the American Society of Nephrology: CJASN*. 2011; 6:2069. [PubMed: 21784825]
18. Gambaro G, Favaro S, D'Angelo A. Risk for renal failure in nephrolithiasis. *American journal of kidney diseases: the official journal of the National Kidney Foundation*. 2001; 37:233. [PubMed: 11157364]
19. Keeley FX Jr, Assimos DG. Clinical trials of the surgical management of urolithiasis: current status and future needs. *Advances in chronic kidney disease*. 2009; 16:65. [PubMed: 19095208]
20. Badawy AA, Saleem MD, Abolyosr A, et al. Extracorporeal shock wave lithotripsy as first line treatment for urinary tract stones in children: outcome of 500 cases. *International urology and nephrology*. 2012; 44:661. [PubMed: 22350835]
21. Preminger GM, Tiselius HG, Assimos DG, et al. 2007 Guideline for the management of ureteral calculi. *European urology*. 2007; 52:1610. [PubMed: 18074433]
22. Al-Abadi E, Hulton SA. Extracorporeal shock wave lithotripsy in the management of stones in children with oxalosis--still the first choice? *Pediatric nephrology*. 2013; 28:1085. [PubMed: 23397522]
23. Kamoun A, Daudon M, Zghal A, et al. Primary hyperoxaluria: Tunisian experience apropos of 24 pediatric cases. *Nephrologie*. 1997; 18:59. [PubMed: 9182235]
24. Daudon M, Estepa L, Lacour B, et al. Unusual morphology of calcium oxalate calculi in primary hyperoxaluria. *Journal of nephrology*. 1998; 11(Suppl 1):51. [PubMed: 9604812]
25. Kerbl K, Clayman RV. Endourologic treatment of nephrocalcinosis. *Urology*. 2000; 56:508. [PubMed: 10962330]
26. Connors BA, Evan AP, Willis LR, et al. The effect of discharge voltage on renal injury and impairment caused by lithotripsy in the pig. *Journal of the American Society of Nephrology: JASN*. 2000; 11:310. [PubMed: 10665938]
27. Boddy SA, Duffy PG, Barratt TM, et al. Hyperoxaluria and renal calculi in children: the role of extracorporeal shock wave lithotripsy. *Journal of the Royal Society of Medicine*. 1988; 81:604. [PubMed: 3184094]
28. Tan IL, Zonderland HM, Boeve ER. Oxalosis provoked by extracorporeal shock wave lithotripsy. *Lancet*. 1994; 344:757. [PubMed: 7915806]
29. Preminger GM, Assimos DG, Lingeman JE, et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *The Journal of urology*. 2005; 173:1991. [PubMed: 15879803]
30. Cochat P, Rumsby G. Primary hyperoxaluria. *The New England journal of medicine*. 2013; 369:649. [PubMed: 23944302]

Figure 1. Retrograde pyelogram (left) and CT scan (right) showing are of nephrocalcinosis (arrow) with no connection to the collecting system.

Table 1

Patient characteristics

	#	(%)	Median	(Range)
Number of patients	149			
Gender				
Male	76	(51)		
Female	72	(49)		
Type of PH				
1	115	(77)		
2	16	(11)		
3	15	(10)		
Unknown	3	(2)		
Age at initial symptom(s) (years)			5.6	(0.1–53)
Age at diagnosis (years)			10.9	(0.1–74)
Diagnosed ≤18 years	97	(65)		
Diagnosed >18 years	52	(35)		
Presenting symptom				
Flank pain/stone	77	(52)		
Hematuria	46	(31)		
Nephrocalcinosis at presentation	36	(24)		
Time from presentation to diagnosis (years)			2.7	(0–62)
Patients with ESRD at presentation	28	(19)		
Patients who developed ESRD during follow-up	34	(28)		
Time from diagnosis to ESRD (years)			15.4	(0.1–51)

PH: Primary hyperoxaluria

ESRD: End staged renal disease

Table 2

Procedures reported by all PH patients

	Number	(%)	Number Patients
Total procedures	362		67
SWL	148	(41)	45
URS	98	(27)	35
PCNL	64	(17)	29
Cystoscopy	21	(6)	15
Open Nephrolithotomy	14	(4)	12
Unknown	17	(5)	5

PH: Primary hyperoxaluria

URS: Ureteroscopy

PCNL: Percutaneous nephrolithotomy

SWL: Shock wave lithotripsy

Table 3

Procedures performed at Mayo Clinic

	#	(%)	Patients	Stone-free rate		
				1° procedure	2° procedure	3° procedure
Total Procedures	54		14	59%	76%	78%
URS	27	(50)	11	57%	65%	
PCNL	15	(28)	7	70%	90%	
SWL	8	(15)	5			
Combine procedures	4	(7)	2			
Ureteroscopy + SWL	2					
Ureteroscopy + PCNL	2					
Complications	6	(11)	4			
Clavien IIIa (Chest tube)	1					
Clavien IIIb (Steinstrasse)	2					
Clavien IVa (ESRD)	3					

URS: Ureteroscopy

PCNL: Percutaneous nephrolithotomy

SWL: Shock wave lithotripsy