Urol Res (2005) 33: 390–393
DOI 10.1007/s00240-005-0483-5

REVIEW

Vernon M. Pais Jr · Dean G. Assimos

Pitfalls in the management of patients with primary hyperoxaluria: a urologist's perspective

Received: 15 January 2005 / Accepted: 14 March 2005 / Published online: 13 November 2005

Abstract The primary hyperoxalurias are rare, inherited diseases which commonly manifest early in life as urolithiasis. As these patients often present to the urologic surgeon, it is imperative that urologists understand the typical presentation, diagnosis, and management of urolithiasis associated with primary hyperoxaluria. In this review, the pertinent epidemiology and pathogenesis as they relate to the diagnosis and natural history of the disease are discussed. The literature on therapeutic options for primary hyperoxaluric patients with calculi is examined, and treatment strategies are suggested.

Keywords Management · Primary hyperoxaluria · Urolithiasis · Epidemiology · Pathogenesis

Introduction

The primary hyperoxalurias are rare monogenic diseases resulting in markedly elevated oxalate excretion, leading to renal stone formation and, in some cases, progressing to end stage renal disease. There are two well characterized disorders, type 1 and type 2 primary hyperoxaluria [1]. Afflicted individuals generally manifest their disease early in life, and nephrolithiasis is the most common initial presentation. Hoppe and Langman reported that in the United States nephrolithiasis was present in 54.4% and nephrocalcinosis in 30% of those with primary hyperoxaluria at the time of diagnosis [2]. Thus, a large number of these patients will be evaluated by urologists. The rarity of these disorders may cause the diagnosis to be overlooked, resulting in a delay in diagnosis. The mean delay in diagnosis in the aforementioned series was 3.4 years with the longest delay being 9 years. Such delays can potentially have a significant impact on quality of life, renal function, and survival. These patients commonly have recurrent stone events and, as a consequence, may need to undergo a number of stone removing procedures. A significant number will have renal failure at the time of diagnosis; 30% in the United States experience [2]. While either renal or combined renal and hepatic transplantation or dialysis may be successful in those who develop renal failure, patients may be at risk for premature death. Saborio and Scheinman reported that in patients with primary hyperoxaluria survival at 6 years was 84% for those undergoing renal transplantation, 56% for combined renal and liver transplantation and 50% for those managed with dialysis [3]. In addition, patients subjected to transplantation are at risk for developing secondary malignancy, infectious problems, and other maladies generated by immunosuppressant medications. The diagnostic pitfalls confronting urologists and potential risks of stone removing procedures will be reviewed in this manuscript.

V. M. Pais Jr · D. G. Assimos (✉)
Department of Urology,
Wake Forest University School of Medicine,
Medical Center Boulevard,
Winston Salem, NC 27157, USA
E-mail: dassimos@wfubmc.edu

Diagnosis

A delay in diagnosis may be due to either failure to evaluate a patient at risk or errors in the evaluation process. Urologists must recognize that children who form kidney stones may be manifesting any of a variety of rare monogenic, inherited disorders of which nephrolithiasis is a mode of phenotypic expression. Such entities and their respective stones include primary hyperoxaluria types 1 and 2 (calcium oxalate), cystinuria (cystine), xanthinuria (xanthine), adenine phosphoribosyl transferase deficiency (2,8-dihydroxyadenine), hypoxanthine-guanine phosphoribosyl transferase deficiency (uric acid), and the calcium channel disorders including Dent's disease, X-linked nephrolithiasis, X-linked hypophosphatemic rickets (calcium oxalate and calcium phosphate stones). While the majority of children with kidney stones in North America have idiopathic calcium

oxalate nephrolithiasis [4], urologists must still be aware that these rare disorders exist. Therefore, a metabolic evaluation should be undertaken to assess for their presence. This also holds true for those patients with coexistent congenital or acquired obstruction of the collecting system. A significant number of these patients will also have underlying metabolic abnormalities which predispose them to stone formation, especially those with recurrent stones. Hussman and associates reported that 15 of 22 (68%) patients less than 17 years of age (median age at diagnosis 11 years) who had ureteropelvic junction obstruction and non-struvite stones developed recurrent stones. Thirteen of these (87%) had an identifiable metabolic abnormality [5]. The importance of underlying metabolic abnormalities in this cohort was also demonstrated by Tekin and colleagues [6]. They noted that the spectrum of metabolic abnormalities in children with ureteropelvic junction obstruction and stones was similar to that of children with stones and normal collecting system anatomy. Moreover, they found that oxalate excretion was greater and citrate excretion was less than that of aged matched controls in both of these cohorts.

Primary hyperoxaluria should be suspected in children with urinary oxalate excretion greater than 1 mmol/1.73m^2 [1]. It is also important to recognize that some patients with primary hyperoxaluria will manifest their disease as adults [7]. Therefore, this diagnosis should be considered in adults with an oxalate excretion greater than 100 mg/day who are not at risk for enteric hyperoxaluria. Hyperoxaluria has been reported in as many as 20% of stone forming children subjected to a metabolic evaluation [4]. Neuhaus and associates found that 11 of 21 hyperoxaluric children whom they evaluated had primary hyperoxaluria [8]. While this high percentage is likely due to their tertiary referral population, it nevertheless underscores the importance of careful evaluation of these patients.

The diagnosis of primary hyperoxaluria is typically initiated with a urinary metabolic profile. Certain errors can be made at this level. The urine may not be collected in an appropriate environment. This can occur if the urine is not properly acidified to prevent deposition of insoluble calcium oxalate. Incomplete collection is another potential source of error. If this is suspected, the utilization of age related oxalate to creatinine ratios is recommended. Failure to express oxalate excretion in children based on adult body surface area may also lead to error. Increased glycolate excretion occurs in patients with type 1 primary hyperoxaluria. However, this is not present in approximately a third of this cohort [1]. Patients with type 2 disease typically have elevated L-gylceric acid excretion, but there are individuals who do not have this phenotypic profile [9]. The diagnosis of either disorder has in the past been confirmed with a liver biopsy from which the activity and immunoreactivity of alanine-glyoxylate aminotransferase (AGT) is assessed for the diagnosis of type 1 disease and glyoxylate reductase/hydroxypyruvate reductase (GRHPR) for the type 2 disorder [10]. Currently, the diagnosis can be made in certain individuals by employing polymerase chain reaction testing of blood to screen for mutations associated with each respective disorder. Rumsby and colleagues described their approach, screening for any of three common mutations in the AGXT gene (c.33_34insC, c508G > A, and c.731T > C) and the c.103delG mutation in the GRHPR gene, which encode AGT and GRHPR, respectively. The c.103delG mutation is found in Caucasians, whereas the c.731T > C mutation is most commonly found in those of Spanish or North African descent. Both the c.33_34insC and c.508G > A mutations can be found across all ethnicities. In PH1, the sensitivity of genetic screening was 62%, as compared with only 33% in PH2. If the patient is homozygous for the mutation or has two different mutations of the gene (compound heterozygote), this is usually sufficient evidence to confirm the diagnosis. However, this occurred in only 34%, such that liver biopsy was required in the remainder [11].

There are also patients who have phenotypic features of primary hyperoxaluria and yet have normal AGT and GRHPR activity. The mechanism of this disorder has not been defined [12]. It is important to recognize this group as they will need specialized care aimed at limiting stone activity.

Management considerations

Upon diagnosis, medical therapy should be instituted. Increased fluid consumption is a cornerstone of management. Patients with PH1 are administered pyridoxine. This results in a significant decrease in oxalate excretion in approximately a third of subjects. Mutations associated with pyridoxine responsiveness have been identified; such findings may allow more specific targeting of therapy [13]. Other agents may be prescribed based on the results of metabolic studies. These may include citrate preparations, neutral phosphates, or allopurinol. Patients with PH2 are managed similarly, although pyridoxine is not utilized. Dietary modification, including limitation of sodium, oxalate, and animal protein, may be employed.

Medical therapy will not treat calculi already formed, and the management of urolithiasis must thus be considered. Symptomatic stone events may require urologic intervention. Children with ureteral stones less than 4 mm in diameter should be given a trial of spontaneous passage, provided symptoms can be adequately controlled and there are no signs of sepsis or risk of permanent renal damage [14]. Larger ureteral stones in children are unlikely to pass and a stone removing procedure will generally be required.

Shock wave lithotripsy (SWL) is an effective treatment for adults and children with renal and ureteral stones [15]. However, a number of issues need to be considered if SWL is contemplated for patients with primary hyperoxaluria. The delivery of shock wave energy to the kidney results in interstitial inflammation

and renal parenchymal hemorrhage due to rupture of small to medium sized arteries and veins [16]. Experiments with delivery of shock wave energy to the porcine kidney indicate that the parenchymal injury affects a larger portion of smaller kidneys [17]. While hemorrhagic changes usually resolve, there remains the potential for permanent renal scarring. Shock wave energy also promotes a transient reduction in renal blood flow and glomerular filtration in the targeted kidney and a decrease in renal blood flow in the untreated renal unit [18]. These changes are more profound in the immature kidney and also in diseased kidneys [19]. Renal growth retardation has been shown in children previously subjected to SWL [20]. There have also been reports of patients with primary hyperoxaluria developing renal functional deterioration after SWL [21–23]. Patients with primary hyperoxaluria tend to form calcium oxalate monohydrate stones [24]. These stones have been demonstrated to be more resistant to SWL [25]. Therefore, these issues need to be taken into consideration before SWL is undertaken in this cohort.

Improvements in ureteroscopic instrumentation and the development of the holmium laser for stone fragmentation have allowed safe and effective treatment of children with ureteral and renal calculi [26]. Stone composition does not limit the utility of the holmium laser [27]. The smaller semi-rigid and flexible ureteroscopes currently available to the practicing urologist facilitate access to ureteral and collecting system stones in children. Dilation of the ureteral orifice is sometimes necessary to allow scope passage. This does not appear to be problematic [26]. A significant number of patients with primary hyperoxaluria have nephrocalcinosis which may be difficult to differentiate radiographically from renal calculi [2]. Ureteroscopy allows the urologic surgeon to directly inspect the renal collecting system, and determine if there are stones within it. This may avert unnecessary SWL or more invasive procedures, as nephrocalcinosis is not typically a ''surgical lesion''.

Percutaneous nephrostolithotomy (PCNL) is a very effective method of removing renal calculi and should be considered in patients with large stone burdens. It has been shown to be safe and effective in both children and adults [28]. Some have advocated performing PCNL using a smaller port of access into the kidney (mini-perc) in an effort to limit renal injury [29]. However, porcine studies have demonstrated that renal scarring does not differ between standard and reduced sized renal access; both resulting in less than a 1% fractional loss of renal parenchyma [30]. However, the mini-perc modification may be helpful for removing stones from kidneys with diminutive collecting systems.

The advent of SWL, ureteroscopic stone removal, and PCNL has dramatically decreased the performance of open surgical stone removal. Even at tertiary referral centers this approach is utilized in less than 1% of patients requiring stone removal [31]. In the primary hyperoxaluria cohort in particular, open stone surgery should be avoided if possible, as there is a risk of promoting renal damage and, ultimately, renal loss. Grateau and colleagues reported on three patients with primary hyperoxaluria in whom renal failure was precipitated by open surgical stone removal [32]. Worcester and associates noted that open stone surgery was the cause of renal loss in nine of 115 (8%) stone forming patients with solitary functioning kidneys [33]. Open stone surgery has been identified as a risk factor for renal insufficiency and renal loss in patients with cystinuria, another inherited stone forming disorder [34]. Anatrophic nephrolithotomy is an open surgical operation utilized to remove large stones from the renal collecting system. Gough and Baillie reported a contemporary series of nine children subjected to this operation. Significant deterioration of renal function occurred in six of the operated kidneys [35].

A modified treatment algorithm should be used for stone removal in patients with primary hyperoxaluria as compared to other patients with nephrolithiasis. While some patients with small stone volumes may benefit from SWL, this should be avoided in those with renal insufficiency and in those with larger stones (>1.5 cm). Computed tomography can be utilized to predict stone fragility. Stones with an attenuation coefficient of greater than 1,000 Hounsfield units are less likely to fragment well with SWL and, therefore, an alternative procedure should be considered [36]. Repetitive treatments should be avoided. Pharmacotherapy and other methods of attenuating renal injury should be considered if SWL is undertaken in this unique cohort [37]. Percutaneous nephrostolithotomy should be undertaken in those harboring larger stones; open surgery for such cases is discouraged. Ureteroscopic laser lithotripsy is a suitable option for those failing SWL and for those with renal stones less than 2 cm in aggregate size. Meticulous metabolic and stone status follow-up is mandatory. A preemptive approach to stone removal may prove to be beneficial. When aggregate stone size in a kidney reaches 1 cm, ureteroscopic laser lithotripsy should be considered, as these patients generally have active stone disease and further stone growth may mandate more invasive therapy.

References

1. Leumann E, Hoppe B (2001) The primary hyperoxalurias. J Am Soc Nephrol 12: 1986
2. Hoppe B, Langman CB (2003) A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. Pediatr Nephrol 18: 986
3. Saborio P, Scheinman JI (1999) Transplantation for primary hyperoxaluria in the United States. Kidney Int 56: 1094
4. Milliner DS, Murphy ME (1993) Urolithiasis in pediatric patients. Mayo Clin Proc 68: 241
5. Husmann DA, Milliner DS, Segura JW (1996) Ureteropelvic junction obstruction with concurrent renal pelvic calculi in the pediatric patient: a long term followup. J Urol 156: 741
6. Tekin A, Tekgul S, Atsu N, Ergen A, Kendi S (2001) Ureteropelvic junction obstruction and coexisting renal calculi in children: role of metabolic abnormalities. Urology 57: 542

7. van Buren M (2000) A stony history. Nephrol Dial Transplant 15: 551
8. Neuhaus TJ, Belzer T, Blau N, Hoppe B, Sidhu H, Leumann E (2000) Urinary oxalate excretion in urolithiasis and nephrocalcinosis. Arch Dis Child 82: 322
9. Rumsby G, Sharma A, Cregeen DP, Solomon LR (2001) Primary hyperoxaluria type 2 without L-glycericaciduria: is the disease under-diagnosed? Nephrol Dial Transplant 16: 1697
10. Milliner DS, Wilson DM, Smith LH (2001) Phenotypic expression of primary hyperoxaluria: comparative features of types I and II. Kidney Int 59: 31
11. Rumsby G, Williams E, Coulter-Mackie M (2004) Evaluation of mutation screening as a first line test for the diagnosis of the primary hyperoxalurias. Kidney Int 66: 959
12. Monico CG, Persson M, Ford C, Rumsby G, Milliner DS (2002) Potential mechanisms of marked hyperoxaluria not due to primary hyperoxaluria I or II. Kidney Int 62: 392
13. Van Woerden CS, Groothoff JW, Wijburg FA, Annink C, Wanders RJA, Waterham HR (2004) Clinical implications of mutation analysis in primary hyperoxaluria type 1. Kidney Int 66: 746
14. Van Savage JG, Palanca LG, Andersen RD, Rao GS, Slaughenhoupt BL (2000) Treatment of distal ureteral stones in children: similarities to the American Urological Association guidelines in adults. J Urol 164: 1089
15. Longo JA, Netto NR (1995) Extracorporeal shock-wave lithotripsy in children. Urology 46: 550
16. Connors BA, Evan AP, Willis LR, Blomgren PM, Lingeman JE, Fineberg NS (2000) The effect of discharge voltage on renal injury and impairment caused by lithotripsy in the pig. J Am Soc Nephrol 11: 310
17. Blomgren PM, Connors BA, Lingeman JE, Willis LR, Evan AP (1997) Quantitation of shock wave lithotripsy-induced lesion in small and large pig kidneys. Anat Rec 249: 341
18. Willis LR, Evan AP, Connors BA, Blomgren P, Fineberg NS, Lingeman JE (1999) Relationship between kidney size, renal injury, and renal impairment induced by shock wave lithotripsy. J Am Soc Nephrol 10: 1753
19. Evan AP, Connors BA, Pennington DJ, Blomgren PM, Lingeman JE, Fineberg NS, Willis LR (1999) Renal disease potentiates the injury caused by SWL. J Endourol 13: 619
20. Lifshitz DA, Lingeman JE, Zafar FS, Hollensbe DW, Nyhuis AW, Evan AP (1998) Alterations in predicted growth rates of pediatric kidneys treated with extracorporeal shockwave lithotripsy. J Endourol 12: 469
21. Ayoub K, Mohamed C, Rachid L (1994) Extracorporeal shockwave lithotripsy in primary hyperoxaluria. Lancet 344: 1365
22. Tan IL, Zonderland HM, Boeve ER (1994) Oxalosis provoked by extracorporeal shock wave lithotripsy. Lancet 344: 757
23. Boddy SAM, Duffy PG, Barrat TM, Whitfield HN (1988) Hyperoxaluria and renal calculi in children: the role of extracorporeal shockwave lithotripsy. J R Soc Med 81: 604
24. Daudon M, Estepa L, Lacour B, Jungers P (1998) Unusual morphology of calcium oxalate calculi in primary hyperoxaluria. J Nephrol 11 [Suppl 1]: 51
25. Williams JC, Saw KC, Paterson RF, Hatt EK, McAteer JA, Lingeman JE (2003) Variability of renal stone fragility in shock wave lithotripsy. Urology 61: 1092
26. Schuster TG, Russell KY, Bloom DA, Koo HP, Faerber GJ (2002) Ureteroscopy for the treatment of urolithiasis in children. J Urol 167: 1813
27. Wollin TA, Teichman JMH, Rogenes VJ, Razvi HA, Denstedt JD, Grasso M (1999) Holmium:YAG lithotripsy in children. J Urol 162: 1717
28. Zeren S, Satar N, Bayazit Y, Bayazit AK, Payasli K, Ozkeceli R (2002) Percutaneous nephrolithotomy in the management of pediatric renal calculi. J Endourol 16: 75
29. Jackman SV, Hedican SP, Peters CA, Docimo SG (1998) Percutaneous nephrolithotomy in infants and preschool age children: experience with a new technique. Urology 52: 697
30. Traxer O, Smith TG, Pearle MS, Corwin TS, Saboorian H, Cadeddu JA (2001) Renal parenchymal injury after standard and mini percutaneous nephrostolithotomy. J Urol 165: 1693
31. Matlaga BR, Assimos DG (2002) Changing indications for open stone surgery. Urology 59: 490
32. Grateau G, Grunfeld JP, Beurton D, Hannedouche T, Crosnier J (1987) Post-surgical deterioration of renal function in primary hyperoxaluria. Nephrol Dial Transplant 1: 261
33. Worcester E, Parks JH, Josephson MA, Thisted RA, Coe FL (2003) Causes and consequences of kidney loss in patients with nephrolithiasis. Kidney Int 64: 2204
34. Assimos DG, Leslie SW, Ng C, Streem SB, Hart LJ (2002) The impact of cystinuria on renal function. J Urol 168: 27
35. Gough DCS, Baillie CT (2000) Paediatric anatrophic nephrolithotomy; stone clearance—at what price? BJU Int 85: 874
36. Joseph P, Mandal AK, Singh SK, Mandal P, Sankhwar SN, Sharma SK (2002) Computerized tomography attenuation value of renal calculus: can it predict successful fragmentation of the calculus by extracorporeal shock wave lithotripsy? A preliminary study. J Urol 167: 1968
37. Benyi L, Weizheng Z, Puyun L (1995) Protective effects of nifedipine and allopurinol on high energy shock wave induced acute changes of renal function. J Urol 153: 596