Primary Hyperoxaluria Type 3 Can Also Result in Kidney Failure: A Case Report

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Primary hyperoxaluria (PH) is a group of genetic disorders that result in an increased hepatic production of oxalate. PH type 3 (PH3) is the most recently identified subtype and results from mutations in the mitochondrial 4-hydroxy-2-oxoglutarate aldolase gene (HOGA1). To date, there have been 2 cases of kidney failure reported in PH3 patients. We present a case of a young man with a history of recurrent urinary tract infections and voiding dysfunction who developed kidney failure at 33 years of age. He developed a bladder stone and bilateral staghorn calculi at 12 years of age. Initial metabolic evaluation revealed hyperoxaluria with very low urinary citrate excretion on multiple measurements for which he was placed on oral citrate supplements. Further investigation of the hyperoxaluria was not completed as the patient was lost to follow-up observation until he presented at 29 years of age with chronic kidney disease stage 4 (estimated glomerular filtration rate 24 mL/min/1.73 m^2). Hemodialysis 3 times a week was started at 33 years of age, and subsequent genetic testing revealed a homozygous HOGA1 mutation (C.973G>A p.Gly325Ser) diagnostic of PH3. The patient is currently being evaluated for all treatment options including possible liver/kidney transplantation. All cases of a childhood history of recurrent urinary stone disease with marked hyperoxaluria should prompt genetic testing for the 3 known PH types. Hyperhydration and crystallization inhibitors (citrate) are standard of care, but the role of RNA interference agents for all 3 forms of PH is also under active study.

Introduction

Primary hyperoxaluria (PH) is a group of genetic disorders that result in an increased hepatic production of oxalate. There are 3 recognized forms of PH, and each demonstrates an autosomal recessive pattern of inheritance. PH types 1 and 2 (PH1 and PH2) are characterized by urinary stone disease beginning early in life, nephrocalcinosis, and often kidney failure. Primary hyperoxaluria type 3 (PH3) is the most recently identified PH subtype and results from mutations in the mitochondrial 4-hydroxy-2-oxoglutarate aldolase gene (HOGA1).

The natural history of PH3 includes recurring kidney stones beginning in childhood, although in contrast with PH1 and PH2, kidney function appears relatively preserved, including those with a diagnosis and/or followed in adulthood. Here we present the case of a man who developed kidney failure at age 33, subsequently leading to a diagnosis of PH3.

Case Report

A 37-year-old man with no known family history of stone disease, kidney disease, or kidney failure had a history of recurrent urinary tract infections (UTIs) beginning at 3 years of age, with subsequent development of daytime enuresis and voiding dysfunction. At 12 years of age, he was diagnosed with a bladder stone together with bilateral staghorn calculi and associated bilateral hydronephrosis. Cystoscopy at that time did not reveal posterior urethral valves, but instead a dilated posterior urethra. He underwent vesicolithotomy and bilateral extracorporeal shock wave lithotripsy. The stones were composed of calcium oxalate monohydrate, calcium oxalate dihydrate, and calcium phosphate. Follow-up imaging revealed a small (2 × 3 mm) stone remaining in the left upper pole, which was treated with shock wave lithotripsy.

His metabolic evaluations consistently revealed marked hyperoxaluria (oxalate excretion of 88-140 mg/d [0.9-1.5 mmol/1.73 m^2]; reference range, <45 mg/d or <0.5 mmol/1.73 m^2) with an unmeasurable citrate concentration. His 24-hour urine calcium was not elevated (54 mg/d [13.5 mmol/L/d]). There was no evidence for distal renal tubular acidosis (to account for the low urine citrate), and he was started on potassium citrate, 10 mEq twice daily.

After the surgeries, his voiding patterns improved, but he continued to experience enuresis, mild stress incontinence, and UTIs. At 16 years of age, a kidney scan demonstrated differential kidney function (66% and 34% in the right and left kidneys, respectively). At 21 years of age, a kidney ultrasound demonstrated bilateral renal atrophy (each kidney 8.9 cm long) with prominent left renal calyces. No concurrent serum creatinine is available.

He was lost to follow-up observation until he presented at 29 years of age with a UTI and was found to have serum creatinine of 3.3 mg/dL (corresponding to an estimated glomerular filtration rate of 24 mL/min/1.73 m^2). Computed tomography imaging demonstrated 1-2 mm stones in both kidneys and bilateral renal atrophy without hydronephrosis or signs of obstruction. He was again lost to follow-up observation until he presented with kidney failure requiring initiation of hemodialysis at age 33. Urologic evaluation demonstrated no postvoid residual urine. Urodynamic studies revealed a normal variant...
Primary hyperoxaluria results from variants of at least 3 different genes that alter glyoxylate metabolism and result in increased hepatic production of oxalate. Humans lack an enzyme capable of degrading oxalate, and the kidneys are in increased hepatic production of oxalate. Humans lack an enzyme capable of degrading oxalate, and the kidneys are not capable of degrading oxalate. The resulting high urinary oxalate concentration promotes the formation of calcium oxalate crystals, kidney stones, and nephrocalcinosis. CKD and kidney failure are well-recognized long-term consequences of prolonged hyperoxaluria.1

Once PH1 patients develop kidney failure, kidney and liver transplantation has been the standard of care; case reports suggest this approach may also be successful for PH2.9,10 Because PH1 accounts for about 80% of PH cases, and was the first subtype to be identified, there are more data on the natural history of PH1. Historically kidney failure occurred in half of PH1 patients by the fourth decade of life, although it has been reported as early as infancy. PH2 accounts for about 10% of all PH cases and on average may have a milder phenotype, but these patients can develop kidney failure and experience recurrent urinary stone episodes beginning in childhood. CKD often occurs and may be progressive, with kidney failure reported in about 25% of patients at last follow-up evaluation.9

PH3, the most recently identified subtype, currently accounts for about 10% of diagnosed PH cases, and results from a defect in the mitochondrial enzyme HOGA, encoded by HOGA1.4 HOGA catalyzes the final step of hydroxyproline metabolism, the conversion of 4-hydroxy-2-oxoglutarate (HOG) to glyoxylate and pyruvate. Hence elevated urinary HOG excretion is a diagnostic biomarker for PH3.7,10 Early PH3 reports suggested that symptom onset was often in early childhood but might lessen with time. However, as experience has developed with this disease, recent evidence suggests that urinary stone episodes are frequent throughout life and all forms of PH.7 To our knowledge, 2 cases of PH3 patients that developed kidney failure have been reported in the literature. The first case occurred in an 8-year-old boy with a solitary kidney who experienced a complicated course after surgical removal of an obstructing stone.15 The second case was of a 78-year-old man who had a lifelong history of urinary stone disease and developed kidney failure after nephrectomy for renal cell carcinoma.12 Stage 2 CKD was also reported in 2 of 7 young PH3 patients, suggesting these patients may be at risk for relatively lower glomerular filtration rate at younger ages.13 Our current case documents a third patient with genetically confirmed PH3 who progressed to kidney failure at 33 years of age. His clinical phenotype of kidney stone disease beginning in early childhood, recurrent stone episodes, hyperoxaluria, and absence of nephrocalcinosis are typical of PH3.

Although the cause of kidney failure in this case may have been multifactorial, progressive damage from oxalate and calcium oxalate crystals likely contributed. Crystal deposition in the renal interstitium may induce an inflammatory response and resulting fibrosis.14 Most patients with PH form calcium oxalate monohydrate stones, as was the case for our patient.7,15 Kidney damage from his large obstructing stones and surgeries may have also contributed to the CKD.

Another consideration is the history from early childhood of bladder dysfunction with a dilated posterior urethral valve. In this setting, frequent urinary tract infections may have been another contributing factor. However, imaging studies after removal of the large staghorn and bladder stone did not demonstrate hydronephrosis, and uroflow at 33 years of age revealed no bladder outlet obstruction. Thus, obstructive uropathy does not appear to have been the sole cause of his eventual kidney failure. The treatment regimens for his hyperoxaluria included high fluid intake and potassium citrate which may have been another contributing factor. However, after that he was lost to follow-up observation for many years, and lack of consistent medical care likely delayed the diagnosis and impacted adherence to the recommended hyperhydration and use of crystallization inhibitors.

The case demonstrates the potential for progressive CKD and kidney failure in PH3. In addition, this case highlights clinical clues to monogenic causes of kidney stones,16 which include onset of stones in childhood, recurring stones, and CKD. Once a monogenic stone disease is suspected, a full metabolic kidney stone evaluation is warranted, which should include measurement of oxalate, citrate, calcium, magnesium, pH, and sodium (Fig 1) in a
24-hour urine collection. If the urine oxalate excretion is increased, urine glycerate (in PH2), glycolate (in PH1), and HOG or 2,4-dihydroxyglutarate (in PH3) can point to a specific PH subtype. Genetic testing for mutations of AGXT, GRHPR, and HOGA1 provides a definitive PH diagnosis and should be pursued if there is any question of the diagnosis.

High fluid intake (>3 L/1.73 m²/d) and inhibitors of calcium oxalate crystallization (citrate or neutral phosphate) have been the standard of care in all types of PH. Until recently, the only methods to reduce oxalate excretion have been pyridoxine in a subset of PH1 patients with specific AGXT mutations and liver transplantation as a means of metabolic correction in both PH1 and PH2. A novel short interfering RNA (siRNA) inhibitor of hepatic glycolate oxidase effectively reduced urinary oxalate excretion in recent clinical trials and has recently been approved for treatment of PH1. In a randomized, double-blind, placebo-controlled multinational trial, this siRNA (lumasiran) reduced 24-hour urinary oxalate excretion by 65% from baseline over the period of 6 months, with 52% of patients experiencing normal or near-normal urinary oxalate excretions at 6 months. A second siRNA agent targeting hepatic lactate dehydrogenase A is currently undergoing clinical trials for PH1, PH2, and PH3.

PH is a rare disease that can result in result in kidney failure. Many patients have already developed CKD or even kidney failure by the time PH is diagnosed. Early diagnosis and treatment is important in reducing stone activity and
prevention of progressive CKD, especially now that novel treatments are emerging. When affected patients develop kidney failure, ongoing hepatic oxalate production in PH requires individualized dialysis management, often 4 or more sessions per week. Careful management of plasma oxalate is necessary in PH1 or PH2 patients at the time of organ transplantation to minimize recurrence in kidney allografts. Thus, diagnosis of PH is imperative for early implementation of traditional and novel therapies that can prevent or delay kidney failure, as well as for effective management of kidney failure should it occur and allow for successful transplantation without recurrent oxalosis.

The risk for CKD in PH3 remains to be determined, but it is possible this risk is greater than previously assumed. The emergence of siRNA therapeutics that could potentially reduce hepatic oxalate production in PH3 highlights the importance of recognizing this disease in order to prevent disease manifestations including frequent stone events and, at least occasionally, CKD and kidney failure.

### References