Primary hyperoxaluria

A frequently unappreciated cause of chronic renal failure[1]

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Primary hyperoxaluria is an inherited autosomal recessive disease leading to renal failure at various ages due to calcium oxalate deposition. Often, frequent stones at an early age are the first manifestation of the disease. Other tissues may be damaged from tissue deposits after renal failure develops. Therapy is directed at providing a normal glomerular filtration rate and oxalate excretion with a functioning graft, combined with measures to reduce oxalate production or precipitation in the urine and kidney. The disease may be a more frequent cause of renal failure than previously recognized and needs to be considered when the clinical findings are suggestive. Although there is an increased risk of recurrence of the disease in the transplanted kidney, with subsequent graft damage and loss, transplantation can be successful in a significant percentage of patients by using techniques that will optimize graft function and reduce the metabolic load of oxalate.

Index terms: Calcium oxalate, urine • Kidney calculi • Kidney failure, chronic • Metabolism, inborn error

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Primary hyperoxaluria is an inborn error of metabolism characterized by the increased production and urinary excretion of oxalate—a nonmetabolized end product of glyoxylate metabolism. Two separate enzyme deficiencies (types I and II) have been identified.

The clinical syndrome is diagnosed by increased urinary excretion of oxalate in the absence of secondary causes for hyperoxaluria. Secondary hyperoxaluria can be caused by intestinal bypass procedures or ileal resection with subsequent increased absorption of oxalate from the colon due

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to binding of calcium within the bowel, excessive dietary intake of oxalate, ethylene glycol poisoning, or pyridoxine deficiency. Primary hyperoxaluria is an autosomal recessive disease present at birth.[1] The heterozygote is generally asymptomatic. Individuals with the disease have an increased production and excretion of oxalate. The initial presentation is generally due to calcium oxalate stone formation. This can occur at infancy (stones develop in 50% of patients before the age of 4 years), later in childhood, or even in an adult. Stones are often large, multiple, and can recur frequently. Some individuals may pass dozens of stones over a period of several years. In addition to complications caused by the formation of stones, calcium oxalate deposition within the renal parenchyma causes damage to the kidney tissue and ultimately results in renal insufficiency and renal failure. This may be associated with radiographic evidence of nephrocalcinosis.

For most individuals who survive past infancy, the amount of oxalate produced is excreted via the kidneys when the glomerular filtration rate (GFR) is normal. Thus, the individual may remain in balance with no significant deposition of calcium oxalate within the kidney or other tissues and organs. Maintaining balance for the increased production of oxalate requires a normal GFR, however. These individuals tend to decompensate when GFR decreases. A decrease in GFR may occur shortly after birth if the enzyme defect is so severe as to cause such an excessive oxalate production that increased oxalate levels in the blood deposits within the kidney. Older individuals may have a decrease in GFR due to calcium oxalate stone formation with subsequent obstruction, infection, or volume depletion. Once a decrease in GFR occurs, normal balance is interrupted due to a decrease in oxalate excretion with continuing oxalate production. This then results in increased levels of oxalate in the blood with subsequent deposition within the kidney. This deposition can lead to a further decrease in GFR, further elevation of the blood oxalate, further deposition in the kidney, further reduction in GFR, and so on. This self-perpetuating cycle can lead to renal insufficiency and renal failure within several months to several years despite the presence of the disease and abnormal oxalate production throughout life. When renal insufficiency and renal failure develop, oxalate excretion in the urine can fall dramatically. This can make diagnosis difficult since oxalate levels in the urine may return to normal at this stage. Also, this results in increasing levels of oxalate in the blood and an increasing positive balance for oxalate. Oxalate can also be deposited in other tissues and organs. Bone, bone marrow, myocardium, and vessel walls may all be extensively damaged due to calcium oxalate deposition, resulting in significant morbidity in these individuals after renal failure develops and when these individuals are maintained on dialysis. Bone-marrow failure with severe anemia, leukopenia and thrombocytopenia,[2] heart failure due to myocardial dysfunction, progressive vascular occlusive disease in the extremities causing ischemia,[3] necrosis,[4] and amputation[4] have all been described.

The extensive tissue deposition of calcium oxalate crystals may make the diagnosis possible even in the presence of advanced renal failure when the urinary oxalate level is not elevated. Blood or serum levels of oxalate (which would be expected to be elevated in renal failure) are generally unreliable due to the fact that even the high levels seen in this disease still represent concentrations near the threshold of sensitivity for the test. Tissue specimens (nephrectomy,[1] bone-marrow biopsy,[5] or biopsies of small vessels[3] or myocardium), however, may document the disease since such deposits are rare or absent in secondary forms of hyperoxaluria.

The course of the disease is severe and rapid after development of renal failure. Fifty percent of individuals die or develop renal failure before the age of 20 years.[6] Once deposition of oxalate begins and progresses in extrarenal tissues, morbidity and mortality may be due to cardiac failure or arrhythmias, vascular insufficiency with ischemia and necrosis, or complications of renal failure and its treatment.

Management of primary hyperoxaluria is difficult and not very successful. Various techniques can be employed to try to reduce the production of oxalate. Large doses of pyridoxine (>1 g/day) may decrease the production in certain individuals due to facilitation of the metabolism of glyoxylate to glycine rather than to oxalate.[7] Thiazide diuretics can reduce calcium excretion in the urine, reducing the risk of calcium oxalate deposition,[8] and may also decrease calcium and oxalate absorption from the intestine. Oral phosphate administration can help reduce calcium absorption due to binding of calcium within the intestine. Magnesium administration can result

in a soluble complex with oxalate in the urine to help reduce the risk of precipitation.[9] Various combinations of these therapeutic modalities have resulted in stabilization of renal function and decreased oxalate excretion in some patients.

When renal failure develops, the condition of the patient often deteriorates rapidly due to oxalate deposition in other tissues. Both hemodialysis and peritoneal dialysis[10,11] have generally been unsuccessful in slowing the progression of the disease, probably due to the low oxalate clearance of these procedures compared to normal renal excretion.

Renal transplantation offers the only significant hope for stabilization of the disease after renal failure develops. Early reports of transplantation in patients with oxalosis documented severe early recurrence of oxalate deposition and loss of graft function within weeks to months.[12–14] In the past, this disease has been considered a contraindication to transplantation. There are several factors that could theoretically predispose patients to early recurrence and graft loss based on the pathophysiology just outlined:

1. Even in the presence of normal graft function, the GFR may be significantly less than normal due to the presence of a solitary kidney compared to two kidneys normally. Children receiving an adult kidney are the exception, and they may be at less risk of recurrence because of this.

2. The early post-transplant period is characterized by various insults that may impair the GFR. These include acute tubular necrosis due to ischemia at harvesting, acute rejection episodes (present in 70%–90% of cadaver recipients), and various drug toxicities and infections. Any reduction in the GFR results in increased blood levels of oxalate, deposition of oxalate within the graft, and further reduction in the GFR.

3. Patients who have been on dialysis for extended periods of time may have built up such a large tissue load of oxalate that, despite a normal GFR, significant oxalate deposition within a kidney occurs.

Thus, it is not surprising that such individuals are at risk of early recurrence of calcium oxalate deposition, renal insufficiency, and graft loss even in individuals who may have been able to manage (with a normal GFR and normal native kidneys) for many years (even into adulthood) prior to renal failure.

It is clear that the best protocol to theoretically optimize the chances of success of renal transplantation include the following:

1. The best graft to optimize GFR should be chosen. Thus, an adult-sized kidney, preferably from a well-matched living related donor, that is least likely to be rejected should be chosen, if possible.

2. Maximum therapy to decrease the risk of calcium oxalate production and deposition in the urine and kidney should be employed. This therapy includes increased urine volume, pyridoxine supplementation, thiazide diuretics to reduce calcium excretion, and phosphate and magnesium supplementation.

Several reports document the possibility of long-term graft function using such protocols.[15–18] One such patient now has normal graft function 18 months after transplantation at the Cleveland Clinic. Although the extrarenal manifestations of the disease might, theoretically, progress following the transplant, the isolated case reports of successful grafts have documented stabilization of these extrarenal manifestations over the short run. The functioning allograft may excrete the metabolic load of oxalate and prevent further accumulation in the tissues. Under the most favorable circumstances, there may be even a net negative balance for oxalate, which would result in a decrease in oxalate deposition within the tissues.

Our experience at the Cleveland Clinic with patients with primary hyperoxaluria illustrates several points of clinical note. Over the last five years, we have seen three patients referred for transplant evaluation with renal failure of uncertain etiology who have subsequently been found to have primary hyperoxaluria. This illustrates the fact that this disease may represent the cause for a significant percentage of cases of end-stage renal failure.[19] Two patients had the diagnosis established by examination of the kidneys at the time of nephrectomy; 1 other patient had the diagnosis established after bone-marrow biopsy. Severe, progressive vascular disease developed in the third patient due to oxalosis with ischemia and necrosis. The patient died before transplantation could be performed.

Two patients underwent a transplant. One patient had been on dialysis for several years prior to transplant, and the graft never functioned, probably due to a combination of acute tubular necrosis and recurrent calcium oxalate deposition documented at nephrectomy. The other patient

had a successful cadaver graft, with immediate function and no rejection episodes, and continues with normal graft function 18 months after the transplant on pyridoxine, hydrochlorothiazide, and increased fluid intake.

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References

1. Boquist L, Lindqvist B, Ostberg Y. Primary oxalosis. Am J Med 1973; **54:**673–681.
2. Breed A, Chesney R, Friedman A, Gilbert E, Langer L, Lattoraca R. Oxalosis-induced bone disease: a complication of transplantation and prolonged survival in primary hyperoxaluria. J Bone Joint Surg (Am) 1981; **63-A:**310–316.
3. Blackburn WE, McRoberts JW, Bhathena D, Vazquez M, Luke RG. Severe vascular complications in oxalosis after bilateral nephrectomy. Ann Intern Med 1975; **82:**44–46.
4. De Hoek CT, Diderich PNM, Gratama S, Wijs-Hofwegen EJM. Oxalosis in chronic renal failure. Proc Eur Dial Transplant Assoc 1980; **17:**730–735.
5. Mathews M, Stauffer M, Cameron EC, Maloney N, Sherrard DJ. Bone biopsy to diagnose hyperoxaluria in patients with renal failure. Ann Intern Med 1979; **90:**777–779.
6. Williams HE, Smith LH Jr. L-glyceric aciduria. A new genetic variant of primary hyperoxaluria. N Engl J Med 1968; **278:**233–238.
7. O'Regan P, Constable AR, Joekes AM, Kasidas GP, Rose GA. Successful renal transplantation in primary hyperoxaluria. Postgrad Med 1980; **56:**288–293.
8. Cunningham E, Oliveros FH, Nascimento L. Metolazone therapy of active calcium nephrolithiasis. Clin Pharmacol Ther 1982; **32:**642–645.
9. Silver L, Brendler H. Use of magnesium oxide in management of familial hyperoxaluria. J Urol 1971; **106:**274–279.
10. Zarembski PM, Rosen SM, Hodgkinson A. Dialysis in the treatment of primary hyperoxaluria. Br J Urol 1969; **41:**530–533.
11. Walls J, Morley AR, Kerr DNS. Primary hyperoxaluria in adult siblings: with some observations on the role of regular haemodialysis therapy. Br J Urol 1969; **41:**546–533.
12. Klauwers J, Wolf PL, Cohn R. Failure of renal transplantation in primary oxalosis. JAMA 1969; **209:**551.
13. Saxon A, Busch GJ, Merrill JP, et al. Renal transplantation in primary hyperoxaluria. Arch Intern Med 1974; **133:**464–467.
14. Toussaint C, Goffin Y, Potvliege P, et al. Kidney transplantation in primary oxalosis. Clin Nephrol 1976; **5:**239–244.
15. Morgan JM, Hartley MW, Miller AC Jr, Diethelm AG. Successful renal transplantation in hyperoxaluria. Arch Surg 1974; **109:**430–433.
16. Whelchel JD, Alison DV, Luke RG, Curtis J, Diethelm AG. Successful renal transplantation in hyperoxaluria. A report of two cases. Transplantation 1983; **35:**161–164.
17. Leumann EP, Wegmann W, Largiader F. Prolonged survival after renal transplantation in primary hyperoxaluria of childhood. Clin Nephrol 1978; **9:**29–34.
18. Scheinman JI, Najarian JS, Mauer SM. Successful strategies for renal transplantation in primary oxalosis. Kidney Int 1984; **25:**804–811.
19. Hricik DE, Hussain R. Pancytopenia and hepatosplenomegaly in oxalosis. Arch Intern Med 1984; **144:**167–168.