

PRIMARY HYPEROXALURIA TYPE I: AN UNDERESTIMATED CAUSE OF NEPHROCALCINOSIS AND CHRONIC RENAL FAILURE IN SAUDI ARABIAN CHILDREN

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Background: Primary hyperoxaluria type I (PHI) is a rare metabolic disease caused by deficiency or abnormalities of the peroxisomal enzyme alanine-glyoxylate aminotransferase. In the majority of patients, the clinical expression of PHI is characterized by recurrent calcium oxalate urolithiasis, nephrocalcinosis and renal failure.

Patients and Methods: Sixteen children aged 5 months to 14 years were diagnosed as PHI over a 10-year period ending in June 1997. The diagnosis was established by quantitative urinary oxalate excretion, or by a high urine oxalate/creatinine ratio on spot urines.

Results: The majority of patients had nephrolithiasis (13/16) and/or nephrocalcinosis (12/16). Four patients already had advanced chronic renal failure at the time of diagnosis. Altogether, PHI accounted for 20% of nephrocalcinosis and 6% of end-stage renal disease. Two patients had a complete response to pyridoxine therapy, while four patients had a partial response. Eight patients underwent organ transplantation, three underwent kidney transplantation, three received combined liver/kidney transplantation for end-stage renal disease, and two received isolated preemptive liver transplantation.

Conclusion: Combined organ transplantation provided the best long-term results.
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Key Words: Primary hyperoxaluria type I (PHI), nephrocalcinosis, nephrolithiasis, end-stage renal disease.

Primary hyperoxaluria type I (PHI) is a rare autosomal recessive disorder of glyoxylate metabolism characterized by increased urinary excretion of calcium oxalate and glycolate. The metabolic defect is caused by deficiency of the hepatic peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT).¹ The latter, with pyridoxine as a cofactor, converts glyoxylate to glycine, thereby reducing glyoxylate to oxalate reaction. Type II hyperoxaluria is a much rarer disorder due to the deficiency of cytosolic D-glycerate dehydrogenase, and it is associated with l-glyceric aciduria.²

The symptoms of PHI are secondary to the deposition of insoluble calcium oxalate crystals in the kidneys and urinary tract, leading to nephrolithiasis, nephrocalcinosis and renal failure in the majority of untreated patients. A rare infantile form of PHI, characterized by massive systemic oxalate deposition, results in chronic renal failure before the first year of life.^{3,4} An unknown number of older children and adult patients presenting with idiopathic

kidney stones, with or without renal failure, may suffer from primary hyperoxaluria.

We report our experience of 16 patients with PHI over the past 10 years to emphasize the role of early diagnosis, aggressive medical management, pyridoxine therapy and organ transplantation in the prevention and treatment of affected patients. PHI appears to be a common cause of nephrocalcinosis and may be an important cause of end-stage renal disease in our population.

Patients and Methods

Sixteen children admitted to King Faisal Specialist Hospital and Research Centre with the diagnosis of PHI form the basis of this report. All patients were first seen over a 10-year period ending in June 1997, and have been followed by at least one of the authors. Every child with nephrourolithiasis/nephrocalcinosis and normal urinary calcium excretion was screened for PHI. During the study period, 60 children were also diagnosed with nephrocalcinosis and 115 with end-stage renal disease.

The diagnosis of PHI was made by either measuring urinary oxalate excretion in 24-hour urine collections, or by spot urine oxalate/creatinine ratio. At least two determinations were made before the diagnosis was confirmed. In two patients with advanced chronic renal

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failure, bone marrow biopsy was helpful in establishing the diagnosis.

Urinary oxalate was measured by an oxalate oxidase-based kit.⁵ Urine glycolate was detected qualitatively by gas chromatography. Once the diagnosis of PHI was established, patients were instructed to drink a minimum of 2 liters of water/m²/day. Medical management consisted of: 1) pyridoxine 5 to 20 mg/kg/day in three divided doses in all patients (mean dose 14 mg/kg); 2) sodium-potassium citrate in ten patients; 3) magnesium citrate in four patients; and 4) phosphate supplements in six patients. Following pyridoxine treatment, urinary oxalate excretion was measured every three to four months. Two patients underwent extracorporeal shock wave lithotripsy (ECSWL) and four patients had surgical removal of ureteric or pelvic stones.

Results

The male/female ratio was 1:1. The median age at presentation was 5 years (5 months-14 years), with 80% of the patients diagnosed before the age of 10 years, and about 66% of those below the age of five. The interval from the onset of symptoms to diagnosis ranged from 0 (screening of asymptomatic siblings) to 4 years, with a median of 18 months.

The clinical findings appear in Table 1. Nephrolithiasis and nephrocalcinosis were present in the majority of patients. PHI accounted for 20% of all cases of nephrocalcinosis diagnosed during the corresponding study period (Table 2). This is considerably higher than those reported in other series.⁶ Four patients with nephrocalcinosis and nephrolithiasis and three with hyperoxaluria were asymptomatic and diagnosed by sibling screening of known patients with PHI. Four patients had advanced chronic renal failure at the time of diagnosis, with variable degrees of systemic oxalosis. Urinary tract infection, abdominal pain and hematuria were relatively common. None of our patients presented with the infantile form of PHI.

The diagnosis of PHI was made by quantitative urinary oxalate excretion in seven patients, where the mean excretion rate was 1.76 ± 0.2 mmol/1.73 m²/24 hr (normal <0.5 mmol/0.173 m²/day).⁷ In seven patients, the diagnosis was made by "spot" urine oxalate/creatinine mmol ratios, with a mean of 0.67 ± 0.17 (normal <0.15).⁷ Glycolic aciduria was present in all four patients tested. In two patients with chronic renal failure and equivocal urinary oxalate excretion, the diagnosis was established by bone marrow aspiration, which showed extensive oxalate crystal deposition in the bone marrow, characteristic of PHI.⁸

Of the four patients presenting with chronic renal failure, three underwent renal transplantation. Two were unsuccessful, with prompt recurrence of hyperoxaluria and death due to complications of systemic oxalosis. One patient received a kidney from a live unrelated donor, and

the second received a cadaveric kidney. The third patient is alive and well, with mild renal impairment four years post-transplantation from a living related donor. The fourth patient died while on hemodialysis awaiting a renal transplant.

Twelve patients, including two with mild renal impairment, were treated with the medical regimen described. Seven have maintained normal or mildly impaired renal function during treatment of up to seven years. Response to pyridoxine was variable, with only six patients (37%) showing a definitive response. Of the remaining five patients, two siblings aged five and eight years, with a strong family history of hyperoxaluria and chronic renal failure in childhood, underwent preemptive liver transplantation. One died from graft vs. host reaction. His sister, currently 12 years old, is alive and well four years post-liver transplantation, and has normal kidney function and normal urine oxalate excretion. The remaining three patients developed end-stage renal disease at ages 9, 10 and 12 years (mean interval from diagnosis 6 ± 1.5 years), respectively. All received liver and kidney transplants and are doing well at 5½, 5 and 4½ years post-transplantation, respectively, and their urinary oxalate excretion remains in the normal range. Organ transplantation data appears in Table 3. Altogether 7 of 16 patients with PHI presented with or developed end-stage renal disease. This represents 6% of all cases of end-stage renal disease diagnosed during the same study period, and is significantly higher than the 1%-2% incidence reported in the Western literature.⁹

Discussion

Primary hyperoxaluria type I is an autosomal recessive disease caused by deficiency of liver-specific peroxisomal enzyme AGT. The latter has been mapped recently to chromosome 2q36-37. Several mutations have been found in the coding region, resulting in 3 main phenotypes: 1) absence of both immunoreactive and catalytic AGT activity detected in 42%; 2) presence of immunoreactive, but absent catalytic AGT activity in 16%; 3) presence of both activities, but with 90% of the AGT mistargeted to the mitochondria instead of the peroxisomes (40%).¹⁰

The clinical manifestations of PHI are due to the excessive urinary excretion of the poorly soluble calcium

TABLE 1. Presenting findings in 16 patients with PHI.

Nephrolithiasis	13
Nephrocalcinosis	12
Urinary tract infection	9
Abdominal pain	7
Asymptomatic (family screening)	7
Hematuria	5
Chronic renal failure	4
Systemic oxalosis	2

TABLE 2. *Nephrocalcinosis in children, KFSH&RC (1988-1997).*

Primary hyperoxaluria	12
Familial renal Mg ⁺⁺ wasting	20
Congenital Cl diarrhea	5
Barter's syndrome	6
Renal tubular acidosis	12
Hypervitaminosis D	5
Total	60

TABLE 3. *Results of organ transplantation in 8 patients with PHI.*

Organ transplanted	Age/sex	Outcome
Kidney	7/F	Failed hemodialysis, death
	7.5/M	Failed hemodialysis; death? no follow-up
	15/M	A/W 4.5 yr post-transplant, Cr C1, 57 mL/min/1.73 m ²
Liver	5/M	Died with GVHD 6 wk post-transplant;
	8/F	A/W 4.5 yr post-transplant, Cr C1, 95 mL/min/1.73 m ²
Liver and kidney	9/F	A/W 5.5 yr post-transplant, Cr C1, 97 mL/min/1.73 m ²
	10/M	A/W 5 yr post-transplant, Cr C1, 63 mL/min/1.73 m ²
	12/F	A/W 4.5 yr post-transplant, Cr C1, 67 mL/min/1.73 m ²

A/W=alive and well.

oxalate crystals, which lead to nephrolithiasis and nephrocalcinosis. Hematuria and urinary tract infections are also common. Untreated, the majority of patients with PHI will develop end-stage renal disease, usually over a short period of time from the start of renal impairment. Over 50% of the children affected are uremic by age 15, and 80% will require renal replacement therapy by the end of their third decade.⁹ The onset of renal failure sets the stage for systemic oxalosis, which is characterized by oxalate crystal deposition in bones, skeletal and cardiac muscle, arteries, retina and other tissues.

The age of presentation of PHI is variable and depends on the disease severity, which may relate to the degree of hyperoxaluria and not the degree of enzyme activity.¹¹ The median age of presentation in our patients was five years (5 months-13 years). Unfortunately, because of the rarity of the disease and hence the lack of suspicion, the diagnosis of PHI is usually delayed. Thus, the median interval between the onset of symptoms and diagnosis in our patients was 18 months. Also, the measurement of urinary oxalate and glycolate is limited to university hospitals and reference laboratories, further adding to diagnostic delays in areas where these are not available. Four of our patients already had chronic renal failure at the time of diagnosis, and all progressed to end-stage renal disease within six months to two years.

The clinical diagnosis of PHI should be considered in any child with a history of urinary tract stones, particularly if associated with nephrocalcinosis, a normal urinary calcium excretion, a positive family history and parental consanguinity. These were present in the majority of our

patients. The diagnosis is confirmed by measuring urinary oxalate excretion (and glycolate if available). In normal individuals, this should not exceed 50 mg (0.5 mmol) per 24 hours. Alternatively, and particularly in an outpatient setting and in patients with renal insufficiency, an elevated urinary oxalate/creatinine ratio (>0.1 mmol/mmol) is considered diagnostic.⁷ Definitive diagnosis of PHI can be made by quantification of AGT activity in hepatic tissue obtained by liver biopsy. This is particularly helpful in anuric children and prior to liver transplantation.¹⁰

The treatment of PHI consists of forced hydration, and urine crystallization inhibitors, such as orthophosphate, magnesium and alkali citrate. Of these, only the latter has shown consistent reduction in calcium oxalate saturation in the urine of patients with PHI.¹² We used different combinations of these inhibitors in most of our patients, but it is hard to assess their efficacy when dealing with a small number of patients without a control group.

Data concerning pyridoxine therapy response in patients with PHI is somewhat confusing, both in terms of the percentage of respondents and the recommended dose. A response to pyridoxine has been reported to be as low as 5%-10%,¹³ and as high as 30%.¹⁴ Recommended dose of pyridoxine ranges from 2 mg/kg¹⁵ to 30 mg/kg/day.⁹ We used a mean pyridoxine dose of 14±4.7 mg/kg in all our patients with PHI, even in those presenting with chronic renal failure. While only two patients normalized their urinary oxalate excretion, another four showed a mean decrease of 30%, compared to baseline values. Pyridoxine response was transient and erratic and considered inconclusive in six patients.

Our series of 16 patients included nine patients from three families, all products of consanguineous parents. In each of these families, the identification of the proband led to the detection of asymptomatic siblings. Thus, a total of seven patients were diagnosed by sibling screening of known patients with PHI. Four had nephrocalcinosis with asymptomatic renal calculi, and three had only elevated urinary oxalate excretion. We believe that early detection of asymptomatic siblings is conducive to a more sensible approach to treatment, and may influence the long-term outcome of the disease by delaying and possibly preventing the occurrence of renal failure. This is particularly true for patients who are pyridoxine-sensitive.

Organ transplantation in patients with PHI is a controversial issue. Kidney transplantation has a considerably lower success rate than with other diseases.¹⁶ Progressive deterioration of graft function is commonly observed due to the rapid accumulation of oxalate deposits. Improved results may be seen with aggressive perioperative hemodialysis, post-transplant urinary dilution, and the use of large living related donor kidneys.¹¹ Isolated renal transplantation should be reserved for older patients with less severe forms of PHI, and an insidious progression to chronic kidney failure.^{17,18} This was demonstrated in our 15-year-old patient who

underwent a successful kidney transplant from his mother. By contrast, the outcome of kidney transplantation in our two younger patients, ages 7 and 7½ was associated with early loss of graft and subsequent death from complications of systemic oxalosis.

Combined Liver Kidney Transplantation

By providing the missing enzyme AGT in its subcellular compartment (peroxisome), liver transplantation is an ideal form of gene therapy for PHI.¹⁹ It is unfortunate that an otherwise healthy recipient liver has to be removed for the sake of one missing or misplaced enzyme, but the results from the published literature are encouraging. Over 60 combined liver/kidney transplants have been performed for PHI, with a respective actuarial graft and patient survival rate of 88% at 1 year and 80% at 5 years.²⁰ An added advantage of the combined organ transplant from the same donor seems to be the protective effect from the liver against immunological loss of the renal graft.²¹ Our three patients who underwent combined organ transplantation have had excellent results, with normal or mildly impaired renal function at five years post-transplantation.

Preemptive liver transplantation should be reserved for PHI patients who are pyridoxine resistant with mild renal impairment and/or a sudden deterioration in renal function.^{13,22,23} Liver transplantation should be performed only after demonstrating deficient AGT activity. Our surviving patient, with isolated liver transplantation, has a normal kidney function 4½ years post-liver transplantation.

In conclusion, PHI may be a more frequent cause of nephrocalcinosis and end-stage renal disease in Saudi Arabia than previously recognized. This is probably due to the fact that as an autosomal recessive disease, its incidence and prevalence are expectedly high, as in other populations with a high rate of consanguineous marriages.⁶ In addition, the mutant gene for PHI could have a higher prevalence than in other populations. Because of the clinical heterogeneity of PHI, early recognition and family screening of index cases is of utmost importance. This can be accomplished by measuring urinary oxalate excretion in any child with urinary tract stones and/or nephrocalcinosis. Early diagnosis should be coupled with intensive medical management, including high doses of pyridoxine. The latter may reduce or normalize urinary oxalate excretion and have a renoprotective effect in some patients. Combined liver/kidney transplantation is a viable therapeutic option for patients who progress to chronic renal failure in spite of aggressive medical management.

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