

Primary hyperoxaluria

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Abstract

Primary hyperoxaluria type 1 is a rare metabolic disorder transmitted as an autosomal recessive disease. It is due to a defect of the peroxysomal hepatic enzyme L-alanine: glyoxylate aminotransferase (AGT). The defect in AGT, which normally converts glyoxylate to glycin, results in an increase of the glyoxylate pool, which is converted to oxalate. The first symptoms occur before one year of age in 15 percent and before 5 years of age in 50 percent. The infantile form is characterized by chronic renal failure due to massive oxalate deposition. In other patients, urolithiasis develops with infections, hematuria, renal colics or acute renal failure due to complete obstruction. End-stage renal failure occurs before 15 years of age in half the cases and the resulting increase of circulating oxalate leads to its deposition in tissues causing cardiac conduction defects, hypertension, distal gangrene, and reduced joint mobility and pain. Hyperoxaluria is associated with increased excretion of glycolate. The absence of AGT activity can be confirmed by liver biopsy. A prenatal diagnosis can be made on liver biopsy or by DNA analysis either using polymorphic markers located in the AGT gene region on chromosome 2q36-37 when the family is informative or looking at the mutation when it has been detected in a sibling. Treatment includes high fluid intake to maintain high urine output above 3 liters/1,73m²/day, pyridoxine supplement (AGT coenzyme) and alkalization of urine. Renal transplantation alone does not correct the metabolic disorder, which will recur in the graft. Combined liver and kidney transplantation is probably the treatment of choice in young children: transplantation should be performed before or very soon after starting dialysis in order to prevent extrarenal complications. Hyperoxaluria type 2 is extremely rare and is due to glycerate dehydrogenase deficiency.

Keywords

Primary hyperoxaluria, calcium-oxalate deposition, Glyoxalate, L-alanine:glyoxalate aminotransferase (AGT).

Disease name and synonyms

- Primary hyperoxaluria
- Oxalosis
- L-Alanine:glyoxalate aminotransferase deficiency

Definition

Primary hyperoxaluria (PHO) is a rare metabolic disorder of autosomal recessive inheritance; it is caused by one of two enzymatic defects, both of which result in markedly enhanced conversion of glyoxalate to poorly soluble oxalate which is then excreted in the urine [1-3]. Glyoxalate is normally metabolized via one of three pathways:

- to glycine, in a reaction catalyzed in part by the hepatic peroxisomal enzyme L-alanine:glyoxalate aminotransferase (AGT); this enzyme is abnormal in type 1 PHO. Pyridoxine (vitamin B6) is an AGT coenzyme.

- to glycolate, in a reaction catalyzed in part by the cytosolic enzyme glyoxalate reductase/D-glycerate dehydrogenase; this enzyme is deficient in type 2 PHO. Patients with this disorder excrete high amounts of L-glyceric acid as well as oxalate [4, 30].

- to oxalate, in a reaction catalyzed by lactate dehydrogenase and by L-g-hydroxy acid oxidase/glycolate oxidase.

Diagnosis criteria

The diagnosis of PHO should be suspected in a patient with recurrent kidney stones, normal urinary calcium and uric acid excretion, calcium-oxalate crystals in the urine sediment, and marked hyperoxaluria in the absence of gastrointestinal disease or the ingestion of megadose vitamin C [1]. Children with type 1 PHO and a glomerular filtration rate (GFR) above 15 mL/min/1.73m² excrete high amounts of both oxalate (as measured by the oxalate oxidase method or chromatographic techniques) and glycolate. Normal urinary oxalate excretion per 1.73 m² is less than 45 mg/day or 0.5 mmol/day; values as high as 135-270 mg/day (1.5-3 mmol/day) can occur in PHO.

The presence of AGT deficiency can be confirmed by liver biopsy. Evaluation of the hepatic tissue includes quantification of enzymatic activity, immunoblotting to analyze the protein, and an immunoelectrophoresis to demonstrate the virtual absence of AGT in peroxisomes. AGT activity is less than 2% of normal in 1/3 of the cases and ranges from 2 to 48% of the normal in the remaining patients [2]. Liver biopsy may be particularly helpful, when urinary glycolate excretion is normal, for children with anuria and prior to hepatic transplantation [5].

Prevalence

French nephrologists were surveyed about type 1 PHO patients in their care between 1988 and 1992. Detailed responses were obtained and 90 cases of type 1 PHO were collected. The average prevalence rate of type 1 PHO was 1.05/1,000,000 and its average incidence rate was 0.12/1,000,000/year [6].

Clinical description

The first symptoms occur before 1 year of age in 15% and before 5 years of age in 50% [7]. The infantile form is characterized by chronic renal insufficiency with massive parenchymal oxalosis; these patients do not develop renal calculi. Older children, on the other hand, present with symptoms of urolithiasis (renal colic, hematuria and urinary tract infection) or, in some cases, complete obstruction with acute renal failure. The calcium-oxalate stones are bilateral and radiopaque on X-ray examination.

Type 1 PHO is responsible for approximately 1% of children with end-stage renal disease which develops in half of the patients by 15 years [7]. The rapidity of the progression is variable, probably being dependent upon residual enzyme activity and the response to pyridoxine.*

When the GFR declines below 25 mL/min/1.73 m², the combination of oxalate overproduction and reduced urinary oxalate excretion results in systemic oxalosis with calcium-oxalate deposition in many tissues, including the heart, blood vessels, joints, bone and retina [1,8]. Among the clinical manifestations that can be seen are:

- cardiac conduction defects and even cardiac arrest;
- distal gangrene and difficulties with vascular access for hemodialysis;
- osteoarticular manifestations are severe in patients who have been on dialysis for more than 1 year. Synovitis leads to reduced joint mobility and pain, while calcium-oxalate precipitates in bone are responsible for bands of increased radiodensity and subperiosteal cortical defects. These changes are most prominent in the metaphyses of long bones and trabecular bones and can lead to pathologic fractures; calcium-oxalate crystal deposits may be found in the retinal epithelium and the macula [9].

Treatment**Minimized renal calcium-oxalate deposition**

The efficacy of treatment for PHO depends upon early diagnosis. At present, a number of modalities may be effective in minimizing renal calcium-oxalate deposition before advanced renal failure, including [1,10].

- Maintenance of high urine output (above 3 L/day/1.73 m²) to decrease the tubular fluid oxalate concentration and diminish intratubular oxalate deposition. A gastric tube may be necessary in young children to maintain this high urine flow during night.

- Avoidance of high oxalate-containing foods, such as tea, chocolate, spinach, and rhubarb.

- A trial of high-dose pyridoxine (mean dose 3.0-3.5 mg/kg). Pyridoxine is an AGT coenzyme that converts glyoxalate to glycine, rather than to oxalate. It lowers urinary oxalate excretion in a few homozygous patients, but is more likely to be effective in symptomatic heterozygotes in whom oxalate excretion may fall by about 10% [10].

- Urinary pyrophosphate, citrate and magnesium, are inhibitors of calcium oxalate precipitation. Thus, calcium-oxalate solubility may be increased by the administration of neutral phosphate (orthophosphate, at a dose of 30-40 mg/kg but higher during the period of skeletal growth), potassium citrate (0.15 g/kg), and/or magnesium oxide (500 mg/day/m²).

- Thiazide diuretics have been tried in an attempt to diminish urinary calcium excretion. Loop diuretics, on the other hand, should be avoided since they enhance calcium excretion.

A prospective study illustrated the potential efficacy of long-term therapy if begun when renal function is still relatively normal [10]. Twenty-five patients with types 1 and 2 PHO were treated with pyridoxine and orthophosphate in the doses indicated above. Oxalate excretion fell by about 10%; this effect plus the increased excretion of inhibitors of crystallization led to substantial reduction of urinary calcium-oxalate supersaturation. The mean GFR decline was only 1.5 mL/min/year, and estimated renal survival was 89% at 10 years and 74% at 20 years. Although there was no control group, previous reports suggested a 20-year renal survival of only 20% in untreated patients.

Thus, long-term therapy with pyridoxine and orthophosphate should probably be tried in most patients with PHO. Orthophosphate should be discontinued if the patient progresses to renal failure to prevent phosphate accumulation and exacerbation of secondary hyperparathyroidism. It has been suggested that citrate also can stabilize renal function in patients with type 1 PHO but its role remains uncertain [11].

Intervention is required when stones obstruct the urinary tract. Percutaneous surgery or nephrostomy are preferred, since surgical removal may precipitate acute renal failure [12].

Renal transplantation

Renal transplantation has been proposed as the treatment of choice for patients who progress to end-stage renal failure, since the rate of oxalate removal with standard hemodialysis or continuous ambulatory peritoneal dialysis is insufficient to prevent systemic oxalate accumulation [1,13-15]. However, the transplant experience in PHO has been relatively disappointing, because renal oxalosis recurs leading to loss of the graft in many patients. Both newly produced oxalate and oxalate mobilized from tissue deposits contribute to the renal deposits. Data from the European Dialysis and Transplant Association (EDTA), for example, showed a three-year graft-survival rate of only 23% for living related donor kidneys and 17% for cadaver kidneys in a review of 98 first transplants for oxalosis [16]. Similarly dismal results were observed in a report of a single center's transplantation experience [17].

However, a number of manipulations (in addition to the above modalities) have been tried to make both preventive therapy of the primary disease and renal transplantation more successful. These include [1,14]:

- aggressive preoperative dialysis (as often as 6 days/week) to deplete the systemic oxalate pool.

- Consideration of early transplantation when the GFR is less than 20 mL/min to minimize systemic oxalate accumulation [9];

- the preferential use of a living-related donor to reduce the risk of early acute renal failure, which will lead to oxalate retention. Some physicians also try to avoid cyclosporine to prevent the frequent nephrotoxicity associated with it [1].

Combined liver-kidney transplantation

Combined liver-kidney transplantation is probably the treatment of choice for children with type 1 PHO with progressive renal disease [1,9-12,18]. The liver provides the missing enzyme, thereby lowering oxalate production to the normal range. This modality should be considered only after AGT deficiency has been confirmed by hepatic biopsy. The outcome may be best if transplantation is performed when the GFR falls to 25 mL/min/1.73 m² in association with marked tissue oxalate deposition. However, gradual resolution of tissue oxalate deposits can be achieved even when transplantation is performed after a relatively long period of dialysis [19-23]. In this setting, increased urinary oxalate excretion may persist for as long as 2 years due to mobilization of tissue stores rather than enhanced production.

The daily urine output should be maintained above 3 L/day/1.73 m² as long as the hyperoxaluria persists. Both citrate and

magnesium supplements should also be given during this period to inhibit crystallization. The European Primary Hyperoxaluria Type 1 Transplant Registry with 61 enrolled patients has shown actuarial graft and patient survival of 88% at 1 year and patient survival of 80% at 5 years [24].

Kidney transplantation alone should currently be limited to adults with the late-onset form of the disease. Liver transplantation alone has been proposed for patients with rapidly progressive disease who still have a GFR above 30 mL/min/1.73 m² [25]. In a case report, for example, the preemptive transplantation of a liver alone from a living-related donor resulted in enhanced renal function in a 22-months-old patient [26].

Etiology

Type 1 PHO is much more common than type 2. The defect in AGT, which normally converts glyoxalate to glycine, results in an increase of the glyoxalate pool available for conversion to oxalate. The AGT gene maps to chromosome 2q36-37 and encodes a 43-kDa protein. A number of different mutations have been identified in the coding region of the AGT genes in type 1 PHO patients. They lead to give rise to at least three different defects:

- absence of both immunoreactive AGT protein and AGT catalytic activity (42%)
- presence of immunoreactive AGT protein and absence of AGT catalytic activity (16%)
- presence of both immunoreactive AGT protein and AGT catalytic activity which can reach nearly 50% of normal values. In these patients, most of the AGT is localized in the mitochondria and not in the peroxisomes (mistargeting phenotype) [27].

Diagnosis methods

The most accurate measurement of the oxalic acid level can be obtained by gas chromatography of urine or with a double enzyme method. Enzyme studies on a liver biopsy can provide a specific diagnosis.

Pregnancy

In a recent survey about outcomes and complications of pregnancy in women with primary hyperoxaluria, No maternal complications were reported in half of the pregnancies. In the remaining pregnancies, the most common complications were hypertension, urinary tract infection, and urolithiasis-associated symptoms. Approximately 75% of the infants had no perinatal problems [31].

Antenatal diagnosis

Prenatal diagnosis can be obtained by evaluating AGT activity in a fetal hepatic biopsy; examination of amniotic fluid is not informative [28]. For previously identified mutations, DNA analysis of chorionic villous samples may be used for screening or for linkage analysis with polymorphic markers located in the AGT gene [29]. DNA analysis can be performed earlier during pregnancy and may avoid fetal liver biopsy.

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