**Medical Progress**

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Primary Hyperoxaluria

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THE PRIMARY HYPEROXALURIAS ARE a group of autosomal recessive disorders involving the overproduction of oxalate. Although the initial recognition of the disease is attributed to Lepoutre, who reported it in 1925, the elucidation of the underlying biochemical abnormalities occurred many years later. This review discusses the major biochemical, genetic, and therapeutic advances that have led to a better understanding of primary hyperoxaluria.

Oxalate, a dicarboxylic acid (HOOC-COOH), is a highly insoluble end product of metabolism in humans. It is excreted almost entirely by the kidney, particularly in the form of its calcium salt, and has a tendency to crystallize in the renal tubules. The main defect of inherited hyperoxaluria is the overproduction of oxalate, primarily by the liver, which results in increased excretion by the kidney. The earliest symptoms among those affected are urolithiasis and nephrocalcinosis, which lead to progressive renal involvement and chronic kidney disease. Renal damage is ultimately caused by a combination of tubular toxicity from oxalate, nephrocalcinosis (with both intratubular and interstitial deposits of calcium oxalate), and renal obstruction by stones, often with superimposed infection. Inflammation has recently been shown to contribute to the progression of chronic kidney disease in animal models of nephrocalcinosis induced by calcium oxalate. Secondary phase of damage that is the result of primary hyperoxaluria occurs when the glomerular filtration rate (GFR) drops to 30 to 45 ml per minute per 1.73 m² of body-surface area and the kidney is unable to effectively excrete the oxalate load it receives. At this point, plasma levels of oxalate rise and exceed saturation, and oxalate is subsequently deposited in all tissues (systemic oxalosis), particularly in the skeleton.

Secondary hyperoxaluria may occur as a result of excess dietary intake or poisoning with oxalate precursors or may be the result of enteral hyperoxaluria. The latter can occur after bowel resection, which can lead to sequestration of calcium in the gut, leaving oxalate in its more soluble sodium form, which is then taken up by the colon. Secondary hyperoxaluria must be ruled out before an investigation for primary hyperoxaluria begins.

**Epidemiology**

The true prevalence of primary hyperoxaluria is unknown. Primary hyperoxaluria type 1, the most common form, has an estimated prevalence of 1 to 3 cases per 1 million population and an incidence rate of approximately 1 case per 120,000 live births per year in Europe. It accounts for 1 to 2% of cases of pediatric end-stage renal disease (ESRD), according to registries from Europe, the United States, and Japan, but it appears to be more prevalent in countries in which consanguineous marriages are common (with a prevalence of 10% or higher in some North African and Middle Eastern nations).
Hydroxypyruvate
NADPH
Cytosol
The New England Journal of Medicine
oxidase (GO) is a potential target for substrate reduction therapy.

not clear why this defect would cause an increase in oxalate levels. Glycolate
Primary hyperoxaluria type 3 results from a defect in HOGA, although it is
deficiency, respectively, and is converted to oxalate by lactate dehydrogenase.
oxaluria types 1 and 2, glyoxylate accumulates as a result of AGT and GRHPR
delineated; they are designated as primary hyperoxalurias 1 and 2, the mechanism is
primarily intrahepatic, present largely in the cytosol of hepatocytes and to a lesser extent in
mitochondria. When there is a deficiency of GRHPR, lactate dehydrogenase metabolizes the
accumulated glycolate to oxalate and the hydroxypropyruvate to glycolate.

Primary hyperoxaluria type 3 (OMIM number, 613616) results from defects in the liver-specific mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA). This enzyme plays a key role in the metabolism of hydroxyproline, and kinetic studies suggest that the forward reaction, in which 4-hydroxy-2-oxoglutarate (HOG) is converted to pyruvate and glyoxylate, is favored. However, it is unclear why this defect would cause an increase in oxalate levels, since impairment of the synthesis of mitochondrial glyoxylate would be expected. One theory is that the substrate HOG breaks down to oxalate either enzymatically or in some other way; another is that HOG inhibits mitochondrial GRHPR.

FORMS OF PRIMARY HYPEROXALURIA

There are three forms of primary hyperoxaluria in which the underlying defects have been identified; they are designated as primary hyperoxaluria types 1, 2, and 3. Each is caused by an enzyme deficiency, and each affects a different intracellular organelle (Fig. 1). Common to all is the overproduction of oxalate. In the case of primary hyperoxalurias 1 and 2, the mechanism is the action of lactate dehydrogenase on the im-
mediate oxalate precursor, glyoxylate. The source of oxalate in primary hyperoxaluria 3 has not been identified.

Primary hyperoxaluria type 1 (number 259900 in the Online Mendelian Inheritance of Man [OMIM] database) is caused by a deficiency of the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), a pyridoxal 5′-phosphate–dependent enzyme that catalyzes the transamination of glyoxylate to glycine. This deficiency results in the accumulation of glyoxylate and excessive production of both oxalate and glycolate. AGT is a stable homodimer, with its N-terminal amino acids wrapped around the adjacent monomer. A common variant, Pro111Leu, creates a stronger N-terminal mitochondrial targeting sequence, which influences the fate of some mutant proteins.

Primary hyperoxaluria type 2 (OMIM number, 260000) is caused by a lack of glyoxylate reductase–hydroxypropyruvate reductase (GRHPR), which catalyzes the reduction of glyoxylate to glycolate and hydroxypropyruvate to d-glycerate. GRHPR has a wide tissue distribution, but it is primarily intracellular, present largely in the cytosol of hepatocytes and to a lesser extent in mitochondria. When there is a deficiency of GRHPR, lactate dehydrogenase metabolizes the accumulated glycolate to oxalate and the hydroxypropyruvate to d-glycerate.

Mutations in AGXT, the gene encoding AGT, result in primary hyperoxaluria type 1. One mutation, Gly170Arg, can lead to significant catalytic
activity in vitro, but in some cases remains at the low end of the normal reference range. This mutation and three others (Ile244Thr, Phe152Ile, and Gly41Arg) unmask the N-terminal mitochondrial targeting sequence of AGT (encoded by Pro11Leu), leading to peroxisome-to-mitochondrion mis-targeting (in which AGT, which normally targets peroxisomes, instead targets mitochondria). At least 178 mutations have been described18; of these, Gly170Arg and c.33dupC occur across populations at a frequency of 30% and 11%, respectively.19 In contrast, the Ile244Thr mutation is especially common in North Africa and Spain.20,21 The only known aspect of primary hyperoxaluria type 1 with a strong genotype–phenotype relationship is responsiveness to pyridoxine, which occurs in patients with the Gly170Arg and Phe152Ile mutations22,23 and is mediated by effects on protein stability, catalytic activity, and peroxisomal import.24 There is no association between age at onset and mutation, and there can be marked intrafamilial clinical heterogeneity.25

A total of 30 mutations have been identified in GRHPR, the gene that is defective in primary hyperoxaluria type 2,18 and 2 of these mutations, c.103delG and c.403_404+2delAAGT, are relatively common; the former occurs exclusively in white populations, the latter almost entirely in Asian populations.9

The association of mutations in HOGA1 with primary hyperoxaluria type 3 has been reported recently,12 and 19 mutations have been described.12,26-28 One particular variant, c.700+5G→T, accounts for half of all mutant alleles.

**CLINICAL SPECTRUM**

Primary hyperoxaluria may occur at almost any age — from birth to the sixth decade of life — with a median age at onset of 5.5 years.29 The clinical presentation varies from infantile nephrocalcinosis and failure to thrive as a result of renal impairment to recurrent or only occasional stone formation in adulthood. However, 20 to 50% of patients have advanced chronic kidney disease or even ESRD at the time of diagnosis.6,29,30 Roughly 10% of patients receive a diagnosis of primary hyperoxaluria only when the disease recurs after kidney transplantation. In other cases, the disease is identified before symptoms appear in the course of family evaluations. Kidney injury, leading to a decrease in the GFR, results in chronic kidney failure and ultimately in ESRD, together with progressive systemic involvement (Fig. 2). The major sites of crystal deposition are the kidneys, the blood-vessel walls, and the bones, with crystal deposits often leading to fractures. Oxalosis can also affect the joints, retina,31 skin, bone marrow,32 heart,33 and central nervous system,34 leading to severe illness and death. Data from the Rare Kidney Stone Consortium indicate that the median age at diagnosis of ESRD is 24 years.35 According to the European pediatric registry, the median age at the initiation of renal-replacement therapy is 1.5 years, and the patient survival rate 5 years after the initiation of renal-replacement therapy is 76%, as compared with 92% among children with ESRD resulting from other conditions. These figures translate into a risk of death for patients with primary hyperoxaluria that is three times as high as the risk for those without the disease.6

Primary hyperoxaluria type 1 is the most devastating subtype, particularly when it occurs in infancy, but patients who have the Gly170Arg or Phe152Ile mutation have a better overall outcome than other patients with type 1 disease, partly because of their sensitivity to pyridoxine.22,36 Patients with primary hyperoxaluria type 2 appear to have a less severe course, although the two disorders cannot be distinguished according to age at onset, and in some instances, primary hyperoxaluria type 2 is initially assumed to be type 1.37 Primary hyperoxaluria type 3 has the least severe course and may be silent or limited to stone formation, sometimes even improving over time.37 Whereas hyperoxaluria persists in primary hyperoxaluria type 3, nephrocalcinosis and chronic kidney failure are uncommon, and systemic involvement has not been reported thus far. Other factors, including environmental factors and modifier genes, may contribute to the clinical heterogeneity of primary hyperoxaluria.

**DIAGNOSIS**

Given its rarity, primary hyperoxaluria may go unrecognized for several years after the onset of symptoms. Considering the possibility of primary hyperoxaluria and pursuing an evaluation that
is in accordance with published algorithms may facilitate earlier recognition.\textsuperscript{38,39}

Because a majority of patients with primary hyperoxaluria present with symptoms related to urolithiasis, assessment of the risk of kidney stones, based on measurements of urinary levels of oxalate, calcium, citrate, sodium, magnesium, and urate, as well as urinary pH and volume, is central to a good evaluation. In patients with primary hyperoxaluria, kidney stones usually consist of more than 95% calcium oxalate monohydrate (whewellite), and they are unusually pale in color and nonhomogeneous in appearance.\textsuperscript{40,41} A finding of oxalate crystals in a kidney-biopsy specimen is also suggestive of primary hyperoxaluria (Fig. 2). In infancy, the chief presenting feature is metabolic acidosis, along with acute renal failure.

The excretion of urinary oxalate is variable, particularly in the first year of life (Table 1), but...
persistently elevated excretion (>0.7 mmol per 1.73 m² per day, or a urinary oxalate:creatinine ratio greater than the reference range for age), in addition to suggestive clinical symptoms and the absence of secondary hyperoxaluria, indicates the need for further evaluation. Not all patients with primary hyperoxaluria have markedly elevated levels of urinary oxalate, but if symptoms are suggestive, an additional evaluation for primary hyperoxaluria should be considered. Measurements of other urinary metabolites, such as glycolate and l-glycerate, are helpful but nonspecific. Levels of glycolate are elevated in two thirds of patients with primary hyperoxaluria type 1 and may also be elevated in patients with type 3. An increased l-glycerate level was formerly regarded as pathognomonic for primary hyperoxaluria type 2, but the level is not invariably elevated. The presence of precursors of HOG has recently been reported in the urine of patients with primary hyperoxaluria type 3, and the development of routine methods for the detection of such precursors may facilitate the diagnosis of primary hyperoxaluria in a wider group of patients who have kidney stones. Whereas urinary calcium levels are typically low in primary hyperoxaluria types 1 and 2, levels in type 3 may vary and in some instances are quite high. Measurement of plasma levels of oxalate should be reserved for patients with stage 3b chronic kidney disease (estimated GFR, 30 to 45 ml per minute per 1.73 m²), since plasma levels remain relatively normal until kidney function is substantially impaired. Attempts have been made to establish a threshold plasma oxalate level that can be used to differentiate between primary hyperoxaluria and kidney failure from any cause. There is considerable overlap in plasma oxalate values among kidney diseases, although in our opinion, values greater than 50 μmol per liter are suggestive of primary hyperoxaluria.

A definitive diagnosis of primary hyperoxaluria in a patient with clinical signs and symptoms requires genetic testing. In the absence of any additional information, it seems reasonable to conduct testing for type 1 first, since it accounts for approximately 80% of cases of primary hyperoxaluria. If there is no genetic evidence of type 1 disease, the next step is to look for mutations indicating type 2 or type 3, which have a similar frequency. The strategy for genetic testing should also take race and ethnic group into account. The disadvantage of limiting testing to genetic studies is the absence of functional analysis (not all genetic variants are pathologic). In addition, deletions may not be detected unless parental studies are also performed. In some cases, the phenotype is typical of primary hyperoxaluria, but no mutation is detected, either because the mutation lies in a promoter or other regulatory sequence or because some other, as yet undefined, metabolic defect is present (i.e., “uncategorized” primary hyperoxaluria). In such cases, a liver biopsy can

| Table 1. Age-Related Reference Ranges of Metabolites in Patients with Primary Hyperoxaluria.* |
|-----------------|-----------------|-----------------|
| **Urinary Excretion** | **Reference Range** | **Source** |
| 24-Hr specimen | | |
| Oxalate, all ages | <45 mg (0.5 mmol)/1.73 m² | Hoppe |
| Glycolate, all ages | <45 mg (0.5 mmol)/1.73 m² | Hoppe |
| Random (“spot”) specimen | | |
| Oxalate:creatinine | | Barratt et al. |
| <1 yr | 11.9–207 μg/mg (15–260 μmol/mmol) | |
| 1 to <5 yr | 8.7–95.6 μg/mg (11–120 μmol/mmol) | |
| 5 to 12 yr | 47–119 μg/mg (60–150 μmol/mmol) | |
| >12 yr | 1.6–63.7 μg/mg (2–80 μmol/mmol) | |
| Glycolate:creatinine | | Barratt et al. |
| <1 yr | 5.4–47.0 μg/mg (8–70 μmol/mmol) | |
| 1 to <5 yr | 4.0–61.4 μg/mg (6–91 μmol/mmol) | |
| 5 to 12 yr | 4–31 μg/mg (6–46 μmol/mmol) | |
| >12 yr | 2.7–27.0 μg/mg (4–40 μmol/mmol) | |
| Glycerate:creatinine | | Dietzen et al. |
| 0 to 5 yr | 12–177 μg/mg (13–190 μmol/mmol) | |
| >5 yr | 19–115 μg/mg (22–123 μmol/mmol) | |
| HOG:creatinine, adults | | Belostotsky et al. |
| 0.1–3.9 μg/mg (0.07–2.8 μmol/mmol) | |

* Actual data are assay-dependent; these data are intended to provide a guide for clinicians. HOG denotes 4-hydroxy-2-oxoglutarate.
be performed to test for levels of AGT and GRHPR activity; if the results are negative, primary hyperoxaluria types 1 and 2 can be ruled out. As yet there is no enzymatic test that can be used to diagnose type 3, although tests showing elevated hepatic levels of HOGA have been described.15

For persons with a family history of primary hyperoxaluria, particularly type 1, genetic screening can be performed, and testing during the first trimester of pregnancy can establish a prenatal diagnosis.47 Preimplantation diagnosis may be possible, depending on local facilities.

**MANAGEMENT**

**SUPPORTIVE MEASURES**

Once a diagnosis of primary hyperoxaluria is being considered, supportive measures should be initiated, since long-term adherence to such treatment can dramatically improve the prognosis and slow the progression to ESRD.48 Fluid intake of more than 2 to 3 liters per square meter of body-surface area per day is essential for stone prevention,39 but in infants tube or gastrostomy feeding may be required to obtain appropriately dilute urine around the clock. Oral potassium citrate (0.10 to 0.15 mg per kilogram of body weight per day) is used to alkalinize urine (ideal pH, 6.2 to 6.8) and, more important, to inhibit crystallization;42 if renal function is impaired, sodium citrate should be used to avoid an increase in the potassium load.49

Pyridoxine supplementation is helpful in primary hyperoxaluria type 1 (but not in other forms of primary hyperoxaluria). A starting dose of 5 mg per kilogram per day may be progressively increased but should not exceed 20 mg per kilogram, with a trial period of at least 3 months.39 Responsiveness is defined as a decrease in the level of urinary oxalate by more than 30% from the point of treatment initiation. As previously mentioned, the Gly170Arg and Phe152Ile genotypes are associated with a significant and sustained reduction of urinary oxalate levels during treatment with pyridoxine, which leads to improvement in the overall prognosis.23 Responsiveness to pyridoxine has also been observed in patients with the Ile244Thr genotype.30 Pyridoxine can be discontinued after 3 months if oxalate levels have not fallen, provided that complete adherence to treatment has been confirmed. The intestinal oxalate load has a limited effect on disease progression in primary hyperoxaluria, since the main source of oxalate is endogenous. Consequently, oxalate-rich foods should be restricted only as a precaution,50 and normal calcium intake should be maintained. Probiotics that break down oxalate (e.g., Oxalobacter formigenes) may have a role in promoting intestinal oxalate excretion,51 although a recent clinical trial had disappointing results.52

Extracorporeal shock-wave lithotripsy (ESWL) is not recommended in patients with primary hyperoxaluria who have a heavy stone burden, both because calcium oxalate stones do not easily fragment53,54 and because the risk of parenchymal damage, particularly in small kidneys, is high (a problem that has been reported in studies of primary hyperoxaluria in animals).55 For affected patients with a high stone burden, minimally invasive methods (e.g., ureteroscopic laser lithotripsy with percutaneous stone removal) are preferable to ESWL.53,56

**DIALYSIS**

Conventional hemodialysis and peritoneal dialysis do not eliminate sufficient levels of oxalate to avert a continuous positive balance (Fig. 2D). Thus, more intensive strategies must be used to clear plasma oxalate levels and to limit systemic involvement.57 If preemptive transplantation is not feasible, therapeutic strategies that include short daily sessions of high-flux dialysis, nocturnal dialysis, or combinations of hemodialysis and nocturnal peritoneal dialysis are needed to keep predialysis levels of plasma oxalate below 30 to 45 μmol per liter.34,58

If a patient who presents with ESRD is found to have primary hyperoxaluria type 1, responsiveness to pyridoxine should be tested, since a pyridoxine-induced reduction in plasma oxalate levels would influence the dialysis strategy.34 Once kidney failure occurs, oxalate deposition in the bone marrow may result in treatment-resistant anemia.59 In addition, oxalate deposition in bone may result in oxalate osteopathy, which in some cases may lead to accelerated bone maturation with reduced final height.60

A multidisciplinary approach is needed to achieve the best possible management of primary hyperoxaluria. Patients and their families may find patient advocacy groups helpful...
(e.g., the Oxalosis and Hyperoxaluria Foundation [www.ohf.org], OxalEurope [www.oxaleurope.org], and Orphanet [www.orpha.net]).

TRANSLANTATION
Since the liver is the sole organ responsible for glyoxylate detoxification, the excessive production of oxalate will continue as long as the native liver is present in patients with primary hyperoxaluria type 1. Thus, preemptive liver transplantation to avoid the complications of systemic oxalosis would appear to be a logical approach, with the surgery planned before the occurrence of stage 4 chronic kidney disease (estimated GFR, 15 to 30 ml per minute per 1.73 m²); this approach does raise ethical issues, given the risk of death associated with the procedure. Kidney transplantation without liver transplantation confers a very high risk of recurrence. Combined liver and kidney transplantation is therefore the treatment of choice for these patients. Kidney transplantation alone may be considered on an individual basis, such as in adults with confirmed responsiveness to pyridoxine. Dual transplantation is a reasonable choice for patients with stage 4 chronic kidney disease, since oxalate retention increases rapidly at this stage of renal dysfunction. In patients with stage 5 chronic kidney disease (estimated GFR, less than 15 ml per minute per 1.73 m²), sequential transplantation, starting with the liver, makes sense because the presence of a new, unaffected liver may permit the use of aggressive dialysis before renal transplantation, which may mobilize some of the systemic oxalate burden and protect the new kidney. Sequential transplantation is also an option when a suitable kidney is not available. Most studies have used transplants from deceased donors, but a living donor for split-liver and kidney transplantation may be considered.

The U.S. registry data on primary hyperoxaluria indicate a 5-year survival rate of 45% for kidney transplantation alone and 64% for dual kidney and liver transplantation; the corresponding rates for children are 14% and 76%, with the low rate of survival after kidney transplantation alone perhaps reflecting the severity of early-onset disease. Hemodialysis or hemofiltration is recommended during and after organ transplantation for recipients who have a heavy systemic oxalate burden, insufficient urine output, or both. There is limited experience with organ transplantation in patients with primary hyperoxaluria type 2; the ubiquitous tissue distribution of GRHPR favors kidney transplantation, but some transplant recipients have undergone oxalate-related graft loss. Primary hyperoxaluria type 3 has not been associated with ESRD thus far.

Urinary oxalate excretion may remain elevated for many years after transplantation because of the slow resolubilization of systemic calcium oxalate and may lead to nephrocalcinosis or renal calculi in the transplant. Consequently, the transplanted kidney must be protected through forced fluid intake and the use of crystallization inhibitors.

The specific multidisciplinary expertise and financial resources required for transplantation and subsequent management of primary hyperoxaluria are often not available in developing countries. As a result, many patients in these countries die, and for infants with severe primary hyperoxaluria, treatment may be withheld or withdrawn.

FUTURE THERAPEUTIC DEVELOPMENTS
Animal models have been developed for primary hyperoxaluria types 1, 2, and 3 (Salido E, Universidad La Laguna, Tenerife, Spain: personal communication). These models do not have the same phenotype as affected humans but are useful in the evaluation of treatments. The underlying problem in primary hyperoxaluria is not the enzyme deficiency itself but the accumulation of precursors, requiring replacement of liver tissue that is sufficient to overcome residual enzyme inactivity. Cell therapy, in which the liver is repopulated with normal hepatocytes, has been shown to be effective in Agxt knockout mice. However, there are still considerable difficulties in clinical applications of this approach to reduce the proliferation of host hepatocytes while boosting that of the transplanted cells. Hepatocyte transplantation has recently been suggested as a potential bridge to orthotopic liver transplantation in patients with primary hyperoxaluria type 1, but this procedure requires standard immunosuppressive therapy and does not fully correct the enzyme deficit. Gene transfer with the use of adeno-associated virus may be an attractive therapeutic option, but the problem of inducing ade-
Calcium oxalate renal stones, nephrocalcinosis, renal failure

Table 2. Features and Treatment of the Inherited Primary Hyperoxalurias.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal location</td>
<td>2q17.3</td>
<td>9p13.2</td>
<td>10q24.2</td>
</tr>
<tr>
<td>Age at onset</td>
<td>All ages, although mostly in childhood</td>
<td>All ages</td>
<td>All ages</td>
</tr>
<tr>
<td>Presentation</td>
<td>Calcium oxalate renal stones, nephrocalcinosis, renal failure</td>
<td>Calcium oxalate renal stones</td>
<td>Calcium oxalate renal stones</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive treatment</td>
<td>Transplantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydration, citrate, pyridoxine</td>
<td>Liver and kidney</td>
<td>Kidney</td>
</tr>
<tr>
<td></td>
<td>Hydration, citrate</td>
<td></td>
<td>Hydration, citrate</td>
</tr>
</tbody>
</table>

Once the diagnosis has been confirmed by genetic testing, aggressive supportive treatment is indicated, followed by an appropriate organ-transplantation strategy if renal function is declining. Future therapeutic developments are aimed at correcting the underlying defects without exposing patients to the lifelong risks associated with organ transplantation.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

SUMMARY

Primary hyperoxaluria should be considered in any patient with a history of recurrent calcium oxalate stones, nephrocalcinosis, or both (Table 2).

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