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12.10 Hereditary disorders of oxalate metabolism: The primary hyperoxalurias 2174

ESSENTIALS Primary hyperoxalurias (PHs) are rare inherited disorders character- ized by an increased endogenous synthesis of oxalate caused by a deficiency in one of several liver enzymes involved in glyoxylate metabolism. The excess oxalate is eliminated from the body by the kidneys. High concentrations of oxalate in the urine increase the risk of calcium oxalate deposition in the kidney (resulting in nephrocalcinosis) and in the urinary tract (leading to urinary stones). Primary hyperoxaluria is characterized by recurring calcium oxalate stones, presenting from early childhood to late adult life. Over time, deposition of calcium oxalate crystals in kidney tissue leads to kidney damage with progressive loss of kidney function. Primary hyperoxaluria type 1 (PH1; alanine–glyoxylate aminotransferase deficiency) is the most severe form with a me- dian age at end-stage renal failure reached during young adult- hood. Patients with PH type 2 (PH2; glyoxylate/hydroxypyruvate reductase deficiency) and PH type 3 (PH3; 4-hydroxy-2-oxo- glutarate aldolase deficiency) may show preservation of kidney function well into adulthood. Systemic deposition of calcium ox- alate (oxalosis) can follow kidney failure and increased plasma oxalate levels. Diagnosis is made by DNA analysis of peripheral blood samples, or more rarely by enzyme assay of liver biopsy tissue. Prenatal diag- nosis can be accomplished in the first trimester by DNA analysis of chorionic villus samples. Treatment relies on high fluid intake, inhibitors of calcium ox- alate crystallization, and, when required, urological procedures for stone removal. Some patients with PH1 respond to vitamin B6 treatment. Management of end-stage renal failure is difficult as dialysis, whether haemo- or peritoneal, cannot match oxalate production. Isolated kidney transplantation places patients at risk of recurring oxalate deposition in the graft in PH1 patients not re- sponsive to vitamin B6. Liver transplantation, usually combined with kidney transplantation, is a curative treatment for PH1 but car- ries significant risks. Introduction Oxalate, hyperoxaluria, and oxalosis Oxalate is an end product of metabolism with no known useful bio- logical function in humans, indeed oxalate can be distinctly det- rimental to complex life forms because of the low

solubility of its calcium salt. The solubility product of calcium oxalate is readily ex- ceeded in urine, resulting in its crystallization and aggregation into calculi. Under physiological conditions oxalate, especially calcium oxalate, is only poorly absorbed from the gut, so a limited amount of the body's oxalate is supplied directly by the diet. Most is de- rived by endogenous synthesis from dietary precursors, or collagen turnover. Most oxalate in the body is removed by urinary excretion. Little appears to be excreted into the gut, but the physiological importance of intestinal elimination, especially in the presence of normal renal function, is unclear. The predominant role of the kidney in oxalate removal makes it the prime target for calcium oxalate deposition (see 'Renal and urinary manifestations'). The reference range for plasma oxalate in health adults is 1 to 3 μmol/litre and urinary excretion is less than 450 μmol/24 h. In healthy children, the 24-h oxalate excretion and random urine oxalate/creatinine ratios vary according to age. However, when normalized for body surface area, urinary excretion rates for chil- dren 2 years or older are similar to those of adults (i.e. <450 μmol/ 1.73 m2 per 24 h). Genetic causes of hyperoxaluria are rare, but can be severe. The number of different genetic causes of hyperoxaluria is un- known. Three monogenic causes of hyperoxaluria have been well- characterized. These are primary hyperoxaluria (PH) types 1, 2, and 3 (PH1, PH2, and PH3). Historical perspectives The condition now recognized as PH was first identified by Lepoutre in 1925. However, it was another quarter of a century be- fore it was described in detail, and it was not until 1957 that it was recognized as a metabolic disorder. The next great leap forward 12.10 Hereditary disorders of oxalate metabolism: The primary hyperoxalurias Sonia Fargue, Dawn S. Milliner, and Christopher J. Danpure

 came in 1968 when Williams and Smith realized that PH was at least two disorders, now known as PH1 and PH2. The enzyme defect in PH2 was recognized at the time, but the defect in PH1 did not emerge until 1986. Since then, advances in understanding of the PHs have been rapid, offending genes having been cloned, and numerous mutations identified. The gene defect associated with PH3 was identified in 2010. Treatments have evolved in parallel with our increased under- standing of the aetiology and pathophysiology of the condition. Until 20 years ago, the outlook for patients with PH was bleak. However, in the past two decades, life expectancy for most patients has improved markedly following the introduction of more rational medical and surgical treatments, of which enzyme replacement therapy by liver transplantation stands out. Many PH patients are alive today who would not be were it not for liver transplantation. Our increased understanding, especially of enzyme genotype–phenotype relation- ships, has led to the exciting prospect of new, possibly mutation- specific, pharmacological treatments in the not too distant future. Aetiology and pathogenesis The primary hyperoxalurias are a group of rare hereditary disorders of which only three, PH1 (OMIM 259900), PH2 (OMIM 260000), and PH3 (OMIM 613616) are well characterized. The three types are simple autosomal recessive disorders of glyoxylate metabolism that result in marked increases in the metabolic production of ox- alate and the resulting deposition of insoluble calcium oxalate in the kidney and urinary tract. Despite these apparent similarities, the molecular bases of these disorders are completely different. PH1 is caused by a de- ficiency of the liver-specific peroxisomal enzyme alanine– glyoxylate aminotransferase (AGT, Enzyme Commission (EC) number 2.6.1.44). PH2 is caused by a deficiency of the more widely distributed cytosolic and mitochondrial enzyme glyoxylate/ hydroxypyruvate reductase (GRHPR, EC 1.1.1.26/79). PH3 is caused by a deficiency of 4-hydroxy-2-oxoglutarate aldolase (HOGA, EC 4.1.3.16), a mitochondrial enzyme, highly expressed in liver and kidney tissues. Biochemical abnormalities The outcome of AGT, GRHPR, or HOGA deficiency is increased synthesis

and urinary excretion of oxalate. In common with all aminotransferases, AGT requires a metabolite of vitamin B6, pyri- doxal phosphate, as cofactor. GRHPR is dependent on reduced nicotinamide-adenine dinucleotide phosphate (NADH) but HOGA does not require a cofactor. AGT normally catalyses the conver- sion of the intermediary metabolite glyoxylate to glycine, but its absence in PH1 allows glyoxylate to be oxidized to oxalate and re- duced to glycolate instead (Fig. 12.10.1). GRHPR normally catalyses the reduction of glyoxylate to glycolate as well as the reduction of hydroxypyruvate to d-glycerate. However, its deficiency in PH2 al- lows glyoxylate to be oxidized to oxalate and hydroxypyruvate to be reduced to l-glycerate (Fig. 12.10.1). HOGA catalyses the conver- sion of 4-hydroxy-2-oxoglutarate (HOG) to glyoxylate and pyruvate. The deficiency of HOGA results in accumulation of HOG. The exact mechanism by which this leads to increased oxalate production is still unclear and may involve inhibition of GRHPR by HOG and/ or conversion of HOG to glyoxylate or oxalate by as yet unknown enzyme(s). Oxalate cannot be further metabolized and can only be removed from the body by renal and, to a lesser degree, gastrointestinal excre- tion. Although glycolate, l-glycerate, and HOG can be further me- tabolized, their increased rate of synthesis in the PHs exceeds their ability to be removed metabolically; hence, large amounts of these metabolites are also removed by renal excretion. In most, but not all, patients, hyperoxaluria is accompanied by hyperglycolicaciduria (in PH1), hyper-l-glyceric aciduria (in X X X X X alanine pyruvate glyoxylate glycine AGT DAO glyoxylate glycolate GO glycolate oxalate hydroxyproline hydroxypyruvate D-glycerate L-glycerate glycoladehyde HOG glyoxylate + pyruvate glycolate elevated in PH1, 2, 3 elevated in PH1 elevated in PH2 DHG elevated in PH3 GRHPR GRHPR HOGA GRHPR Hepatocyte Urine LDH cytosol LDH p er o xi so m e m it oc h o n d ri o n Fig. 12.10.1 Main pathways of glyoxylate metabolism in human liver cells. The ‘X’ indicates the location of the enzyme defects in primary hyperoxaluria type 1, 2, or 3. The membranes are likely to be permeable to most or all of the metabolites shown (dotted lines). AGT, alanine–glyoxylate aminotransferase; DAO, d-amino acid oxidase; DHG, dihydroxyglutarate; GO, glycolate oxidase; GRHPR, glyoxylate/hydroxypyruvate reductase; HOG, 4-hydroxy-2-oxoglutarate; HOGA, 4- hydroxy-2-oxoglutarate aldolase; LDH, lactate dehydrogenase; PH1, primary hyperoxaluria type 1; PH2, primary hyperoxaluria type 2, PH3, primary hyperoxaluria type 3.

section 12 Metabolic disorders 2176 PH2), or elevated concentrations of HOG and dihydroxyglutarate (DHG) in PH3. Concomitant hyperoxaluria and hyperglycolic aciduria used to be considered pathognomonic of PH1, and concomitant hyperoxaluria and hyper-l-glyceric aciduria path- ognomonic of PH2. However, up to one-quarter of PH1 pa- tients do not exhibit hyperglycolicaciduria, and some PH2 patients do not have hyper-l-glyceric aciduria. In PH3 elevated concentrations of HOG and DHG, a metabolite of HOG, are found in the urine. Although glycolate and l-glycerate are useful in the differential diagnosis of PH1 and PH2, they themselves appear to cause no ill effects. All the pathological sequelae of the PHs are associated with the increased synthesis and excretion of oxalate. Molecular genetics The phenotype of PH1 is heterogeneous both at a clinical and at a molecular level. Three major enzymic categories are recognized: (1) absence of both AGT catalytic activity and AGT immunoreactive protein, (2) absence of AGT catalytic activity but the presence of AGT immunoreactive protein, and (3) presence of both AGT catalytic activity and AGT immunoreactive protein. Surprisingly for a recessive disease, many patients in the last category can have AGT activity similar to that found in asymptomatic heterozygotes. In most of the latter patients, disease is caused by a protein traf- ficking defect in which AGT is mistargeted from its normal loca- tion in the peroxisomes to the mitochondria. Although mistargeted AGT is still enzymically active, it is unable to fulfil its metabolic

function (i.e. glyoxylate transamination) properly when located in the mitochondria. AGT is encoded by the AGXT gene, which contains 11 exons, spanning approximately 10 kb on chromosome 2q37.3. More than 200 mutations and polymorphisms have been identified at the AGXT locus, the three most common of which are described in Table 12.10.1. Many mutations in AGXT, including some of the most common, segregate and functionally interact with a very common polymorphism that results in a Pro11Leu amino acid replacement. GRHPR is encoded by the GRHPR gene, which contains nine exons and spans approximately 9 kb in the pericentromeric re- gion of chromosome 9. HOGA is encoded by the HOGA1 gene, lo- cated on chromosome 10q24.2, containing seven exons, spanning 27 kb. Rather fewer mutations have been found at the GRHPR and HOGA1 loci. Structural biology The X-ray crystal structures of AGT (Fig. 12.10.2), GRHPR, and HOGA have been determined, enabling the effects of many of the missense mutations and, in the case of AGT, their interactions with the Pro11Leu polymorphism to be rationalized. The most common muta- tion found in PH1, with an allelic frequency of 30 to 40% in Europeans, leads to a Gly170Arg amino acid replacement. This mutation, to- gether with the common Pro11Leu polymorphism, is responsible for most cases of AGT peroxisome-to-mitochondrion mistargeting. The Pro11Leu polymorphism generates a functionally weak N- terminal mitochondrial targeting sequence, the efficiency of which Table 12.10.1 The most common mutations and polymorphisms found in alanine–glyoxylate aminotransferase, glyoxylate reductase, and 4-hydroxy-2-oxo glutarate aldolase in European and North American populations Polymorphism/ mutation Description Allelic frequencya PH1 patients (%) Normal populationa (%) AGXT polymorphisms Pro11Leub, c Substitution of proline by leucine at residue 11 c.50 15–20 Intron 1 duplicationc A 74-bp partial duplication of intron 1 c.50 15–20 Ile340Metc Substitution of isoleucine by methionine at residue 340 c.50 15–20 AGXT mutations Gly170Argb, d Substitution of glycine by arginine at residue 170 30–50 33–34dupC Insertion of a single base (C) leading to a frameshift c.12 Ile244Thrd, e Substitution of isoleucine by threonine at residue 244 6–9 PH2 patients (%) GRHPR mutations c.103delG Frameshift, premature stop codon c. 35 c.403_404+2del Mis-splicing 18 PH3 patients (%) HOGA1 mutations Glu315del In frame deletion of glutamine residue 31 c.700+5G>T Mis-splicing 49 PH1, primary hyperoxaluria type 1; PH2, primary hyperoxaluria type 2; PH3, primary hyperoxaluria type 3. a In European and North American populations. b Pro11Leu and Gly170Arg synergistically interact to misdirect AGT from its normal location in hepatocyte peroxisomes to mitochondria. c These three polymorphic variations together define the minor AGXT allele. d Mutation segregates with the minor allele of AGXT. e Ile244Thr has a much higher frequency in some North African and Spanish populations.

 is enhanced by the additional presence of the p.Gly170Arg muta- tion. Interestingly, the Gly170Arg mutation on its own is predicted to be without any untoward consequences, at least in vitro. Other AGT mutations have been shown to be able to result in mitochondrial mistargeting in in vitro systems, although only the p.Phe152Ile muta- tion is known to do so in PH1. Other forms of primary hyperoxaluria There are other forms of PH in addition to PH1, PH2, and PH3. These are indeterminate in number and poorly characterized. Case studies have been published of individuals with elevated urinary oxalate of presumed metabolic origin, but who have normal AGT and GRHPR activities, or absence of mutation in any the genes responsible for PH1, PH2, and PH3. Potential ex- planations of the basic defects in these non-PH1, non-PH2, or non-PH3 patients have included dysfunction of other metabolic enzymes involved indirectly in oxalate synthesis, abnormalities in enteric oxalate absorption, and defects in renal oxalate excre- tion, but no conclusive proof has

been forthcoming for any of these possibilities. Epidemiology The PHs are rare disorders which account for 1 to 10% of cases of paediatric end-stage renal disease depending on the country. In Europe, PH1 has an estimated prevalence of 1.0 to 2.9 per mil- lion people and an incidence of 0.12 to 0.15 per million per year. However, both prevalence and incidence are likely to be greater in populations with a high frequency of consanguinity. There are limited data available regarding the prevalence or inci- dence of PH2 or PH3. However, within the population of patients with PH, PH1 represents 70 to 80% of patients, with PH2 and PH3 representing approximately 10% each.
A recent analysis of carrier frequency in the general population suggests that PH is under-diagnosed and/or incompletely penetrant, especially for PH3. Specific mutations frequencies vary between ethnic groups in all three PH types. Clinical features Renal and urinary manifestations PH presents with symptoms related to urolithiasis, usually in child- hood but sometimes in adult life. Recurring stone formation is characteristic, as is progressive kidney damage, especially in PH1 patients who advance to end-stage kidney failure at a median of 25 to 35 years of age in European and North American populations. There is better preservation of kidney function overall in PH2 and PH3. With progressive loss of kidney function, a rising plasma ox- alate concentration leads to deposition of calcium oxalate in many organs (systemic oxalosis) (see ‘Systemic oxalosis’). Variability of clinical expression is marked, with some patients reaching end-stage renal failure in early childhood, while others retain renal function into late adulthood. High concentrations of oxalate in the urine result in the forma- tion of calcium oxalate crystals that attach to the renal tubule epi- thelium. The crystals are then endocytosed by renal tubule epithelial cells and migrate to the renal interstitium. There, the crystals incite an inflammatory, giant-cell reaction that results in renal injury, ul- timately leading to interstitial fibrosis. Widespread calcium oxalate deposition in the renal parenchyma is termed nephrocalcinosis and is usually visible on renal imaging studies. Aggregation of cal- cium oxalate crystals in the urinary space leads to stone formation (nephrolithiasis or urolithiasis). For reasons that remain poorly understood, infants and young children appear more likely to de- velop nephrocalcinosis, although it can occur at any age. Stones in the absence of nephrocalcinosis are more characteristic in older children and adults. Although marked hyperoxaluria is present from early infancy, the age at which symptoms develop is highly variable, ranging from a few months to late adulthood. In most patients, symptoms or find- ings related to urolithiasis (pain, haematuria, stone passage) are evi- dent in early childhood. Recurring stone formation is characteristic, often requiring multiple stone removal procedures. Over time, the damaging effects of calcium oxalate deposition in the kidney, epi- sodes of transient obstruction due to stones, and injury related to stone-removal procedures or infection result in irreversible loss of renal function. End-stage kidney failure can occur at any age, from infancy to the sixth decade of life, with a median of approximately 30 years in PH1 (Fig. 12.10.3). End-stage kidney failure is also pos- sible in patients with PH2 or PH3, despite being considered milder forms of PH. In a few patients, the first clinical manifestation of PH is kidney failure, with symptoms of uraemia prompting medical attention. On evaluation, nephrocalcinosis and/or bilateral renal stones are usually found. Occasionally, the diagnosis is made on renal biopsy in a pa- tient in whom PH was not considered on clinical grounds. A severe infantile form of PH1 results in irreversible kidney failure during the first year or two of life, presenting as failure to thrive. Systemic oxalosis When kidney function falls below a GFR of about 30 to 35 ml/ min per 1.73 m2, the kidney is unable to excrete the excess oxalate produced by the liver and the plasma oxalate concentration begins to rise abruptly. When the calcium oxalate product in plasma ex- ceeds saturation, calcium oxalate crystals are deposited in many Fig. 12.10.2 Crystal structure of human alanine–glyoxylate aminotransferase. PLP, pyridoxal phosphate in orange. Proline residues in position 11 are shown on

the N-terminal arms. Residues with known pathological mutations in red (G41R, F152I, G170R, I244T).

section 12 Metabolic disorders 2178 organs and tissues (systemic oxalosis), resulting in progressively severe multisystem disease. Painful, nonhealing ulcers of the skin, fracturing osteodystrophy, refractory anaemia, complete heart block, and heart failure due to oxalate cardiomyopathy are features of systemic oxalosis. Without prompt and definitive management, death ensues. Differential features There are no clinical features that can reliably differentiate among the three PH types in an individual patient, but PH2 is characterized by slightly lower oxalate excretion rates, fewer stone episodes, and better preservation of renal function than PH1. PH3 patients have an earlier onset of symptoms but lower oxalate excretion rates and slower progression of disease. Though symptomatic stones are not infrequently encountered in infants and young children with PH3, the frequency of stone events may improve during follow-up. There are rare reports of kidney failure in PH3, which may be related to complications of urolithiasis. Differential diagnosis Hyperoxaluria is a well-recognized risk factor in the common condition of idiopathic calcium oxalate kidney stone disease. Although its causes in such patients remain unclear, they are almost certainly multifactorial in nature, with both environ- mental and genetic components (see Chapter 21.14). Anything that increases the body’s burden of oxalate, or elevates the con- centration of oxalate in the urine, increases the risk of calcium oxalate deposition in the kidney and/or urinary tract resulting in nephrocalcinosis and/or urinary stones. Environmental causes of hyperoxaluria include excessive dietary intake of oxalate (par- ticularly when combined with low calcium intake) and extended periods of dehydration. Intake of oxalate precursors, such as intravenous ascorbic acid in patients receiving parenteral nutri- tion, or accidental ingestion of ethylene glycol, is occasionally responsible. Enhanced gut absorption of oxalate is often encoun- tered in patients with gastrointestinal disease or after small bowel resection. Malabsorptive gastric bypass procedures, performed for management of obesity, are emerging as an increasingly frequent cause of enteric hyperoxaluria. Hyperoxaluria is also encountered in patients receiving medications that alter fat absorption, such as tetrahydrolipstatin (orlistat). Clinical investigations PH should be considered in any child with urinary tract stones or nephrocalcinosis and in adults with recurrent calcium oxalate stones, especially if the clinical history extends back into childhood. Impaired renal function in a patient with calcium urolithiasis or nephrocalcinosis, or in a sibling, should also suggest the diagnosis. A presumptive diagnosis of PH can often be made on the basis of urinary oxalate, glycolate, l-glycerate, and HOG/DHG excre- tion. Due to highly age-dependent normal ranges in young children, random urine oxalate/creatinine ratios are best regarded as an initial screen. If the ratio appears elevated, a timed (12–24-h) urine collec- tion should be obtained for more reliable diagnostic information. Repeating the measure on at least three occasions can be useful to help with false positives (as in the case of small children) and false negatives. It should be kept in mind that urinary oxalate excretion can be misleadingly low in patients with advanced renal failure, and concomitant hyperglycolic aciduria (in PH1) or hyper-l-glyceric aciduria (in PH2) is not always present. Urinary HOG and DHG are elevated in patients with PH3, though their diagnostic sensitivity and specificity remain to be established. Plasma levels of oxalate, glycolate, and glycerate are rarely of diagnostic benefit in patients whose renal function is well maintained, though they can be valu- able in those with renal failure. Plasma oxalate concentrations are often increased in patients with end-stage renal disease from causes unrelated to PH, although the degree of elevation in this setting is typically modest. Definitive diagnosis requires confirmation of homozygosity or compound heterozygosity for known mutations of AGT, GRHPR or HOGA, or the

determination of either AGT (PH1) or GRHPR (PH2) enzyme activity on a percutaneous needle biopsy of the liver. The identification of more than 200 mutations in PH1 allows the possi- bility of diagnosis by DNA analysis in suitable families. It has been estimated that, even in the absence of family history, screening pos- sible European or North American PH1 patients for the three most common mutations (Table 12.10.1) would be able to diagnose PH1 with an efficiency of 34%. When coupled with family and linkage analysis studies the success rate is greatly improved. Increasingly, more comprehensive gene sequencing is being used, leading to im- proved diagnostic efficiency, with mutations in AGXT, GRHPR, or HOGA1 found in approximately 90% of patients with PH symptoms. The urinary profile of PH-related metabolites (glycolate, l-glycerate, HOG, DHG) can be used to target the initial genetic testing. In pedigrees with a known mutation, screening of family members is straightforward. The determination of AGT (for PH1) or GRHPR (for PH2) activity on liver biopsy, is now mostly reserved for diagnosis confirmation 100 80 60 40 p<0.0001 PH1 PH2 PH3 NMD 76% (129) 43% (49) 60 40 20 Age (y) Renal Survival (%) 100% (18) 82% (11) 96% (12) 96% (8) 100% (14) 100% (12) 12% (7) PH2 PH3 NMD PH1 66% (4) 96% (4) 100% (7) 20 0
Fig. 12.10.3 Renal survival in primary hyperoxaluria. Kaplan–Meier renal survival plot of patients with PH1 (blue), PH2 (red), PH3 (green), and PH patients with no mutation detected (NMD, black). The lower table shows renal survival estimates with number of patients at risk in parentheses. Source data from Hopp K, et al. (2015) Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. JASN. 2015 Oct;26(10):
2559–70.

 or exclusion in the absence of mutations of any of the three genes involved. Prenatal diagnosis relies on DNA (mutation or linkage) ana- lysis of material obtained from chorionic villus samples in the first trimester. Treatment There are no international guidelines for the specific treatment of PH and recommendations are based on expert opinions. The man- agement initially involves maintenance of high fluid intake; medi- cations to inhibit calcium oxalate crystallization and decrease oxalate production, with use of pharmacological doses of pyridoxine (vitamin B6) for some PH1 patients; and urological procedures and support for end-stage renal failure as required. Treatments that target reduction of calcium oxalate crystal or stone formation, either in the urine or in the blood and body tis- sues (in patients with end-stage kidney disease) are suitable for all types of PH, whereas those addressing enzyme dysfunction are more likely to be disease specific (Fig. 12.10.4). Diet and fluids Decreasing dietary oxalate in PH is of limited use since the main source of oxalate is endogenous. Calcium intake should remain normal as it binds intestinal oxalate. Excessive vitamin C intake should be avoided, especially in end-stage renal disease, as ascorbic acid can be broken down to oxalate. Patients with PH who have adequate renal function should main- tain a high oral fluid intake in order to keep oxalate in the urine as dilute as possible. A suitable target level is 2 to 3 litres/m2 body sur- face area, distributed throughout the day, using the lower range for most adults. In infants and young children, placement of a feeding or gastrostomy tube may be needed to assure sufficient intake and in situations of high fluid loss or limited oral intake, intravenous fluids may be required to maintain hydration in PH patients. Pharmacological treatments Reduction in calcium oxalate crystal formation can be accomplished by lowering the urine oxalate concentration and by the use of medi- cation. Urine alkalinization with citrates, either as sodium citrate (0.1–0.15 g/kg per day) or equivalent doses of either sodium or po- tassium citrate, reduce the degree of calcium oxalate saturation in the urine. Other inhibitors of crystallization may be used such as neutral phosphates (providing 20–30 mg/kg per day of elemental phosphorus in

divided doses) to increase the excretion of pyrophos- phate ions, which inhibit heterogeneous calcium oxalate crystal nucleation, seeded growth, and aggregation. Magnesium supple- ments (e.g. magnesium oxide 200 mg/day in adult patients) may also inhibit crystal growth and aggregation. The doses used should be sufficient to produce a material increase in the urinary excretion of either phosphate or magnesium. Phosphate and magnesium should be avoided if there is renal insufficiency. In about one-third of PH1 patients, pharmacological doses (5– 8 mg/kg per day, <20 mg/kg per day) of pyridoxine (vitamin B6) cause a significant (>30%) reduction in urinary oxalate levels and improvement in clinical condition. Pyridoxal phosphate, a metab- olite of pyridoxine, is the cofactor for AGT, and acts both to in- crease the enzymatic activity of AGT and as a chaperone to help AGT folding and targeting. Patients carrying the p.Gly170Arg or p.Phe152Ile mutations have been shown to be able to respond to pyridoxine treatment, although to varying degrees. Some who are homozygous for p.Gly170ARg demonstrate normalization or near normalization of urine oxalate excretion while receiving pyridoxine. PH1 AGXT (Vit B6) Gene mutation Protein folding targeting Enzyme functional deficiency AGT GR HOGA Gene therapy Chemical chaperones Enzyme replacement therapy: liver transplantation Treatments aimed at causes of PH Symptomatic treatments Substrate depletion (GO, HypDH) Reducing Oxalate synthesis (LDH) Oxalate degradation Hydration Crystallization inhibitors Lithotripsy Surgery Dialysis Kidney transplantation Increased glyoxylate Increased oxalate synthesized Elevated oxalate excretion Ca Ox crystals Ca Ox stones Renal failure GRHPR HOGA1 PH2 PH3 Fig. 12.10.4 Current and future approaches to the treatment of primary hyperoxaluria types 1 (PH1), 2 (PH2), and 3 (PH3). Current and potential treatments are indicated below the respective molecular and pathophysiological step targeted for PH1, PH2, and PH3. Treatments aimed at the pathways on the left tend to be directed at the causes of disease and are usually specific for each type of primary hyperoxaluria (vitamin B6 is specific to PH1). The treatments for the pathway on the right are aimed at the clinically observable symptoms and are likely to be common to all three types. AGT, alanine–glyoxylate aminotransferase; CaOx, calcium oxalate; GO, glycolate oxidase; GRHPR, glyoxylate/hydroxypyruvate reductase; HOGA, 4-hydroxy-2-oxoglutarate aldolase, HypDH, hydroxyproline dehydrogenase. HOGA is expressed in both liver and kidney so that liver transplantation would not necessarily be the only enzyme replacement strategy.

section 12 Metabolic disorders 2180 There are indications that other mutations may also benefit from pyridoxine treatment. A formal testing of pyridoxine responsiveness during a 3-month trial with urinary oxalate measurements before and after initiation of pyridoxine is recommended for all PH1 pa- tients. Pyridoxal phosphate is not required for the activity of GRHPR or HOGA, hence pyridoxine is ineffective in PH2 and PH3 patients. Radiological and surgical interventions Obstructive uropathy requires prompt stent placement or per- cutaneous nephrostomy to relieve the obstruction. For PH pa- tients, minimally invasive methods are preferred in dealing with stones. Endoscopic procedures methods including semi-rigid ureterorenoscopy (URS), flexible ureterorenoscopy (RIRS), and per- cutaneous nephrolithotomy (PCNL) are techniques used with suc- cess, with endoscopic lithotripsy using ultrasonic, electrohydraulic, and laser techniques. Extracorporeal shock wave lithotripsy (ESWL) is also used. Open lithotomy for large calculi has become exceptional. Stone debris may require either external drainage via a nephrostomy or internal drainage via a stent, although stents and other foreign bodies in the urinary tract may rapidly become en- crusted with calcium oxalate deposits. Close follow-up is essential with regular radiological and/or ultrasonographic assessment, the aim being to keep the kidneys as free from stones as possible while minimizing repeated ESWL or invasive procedures. Renal

replacement therapy In most patients, haemodialysis and peritoneal dialysis are not cap- able of preventing progression of systemic oxalosis. Combined liver and kidney transplantation—the treatment of choice in patients with PH1 who do not respond well to pyridoxine and are approaching end-stage renal failure—entails its own significant risks. Management of end-stage renal failure is difficult. The high rate of oxalate synthesis most often exceeds achievable rates of its removal, even with intensive haemodialysis regimens or combined haemo- and peritoneal dialysis. The condition of patients with renal failure progressively worsens as calcium oxalate is deposited throughout the body (systemic oxalosis). Kidney transplantation can resolve the uraemic consequences of kidney failure and reduce plasma oxalate concentrations to levels that fall below the supersaturation threshold for calcium oxalate. However, kidney transplantation alone is problematic in PH1: pa- tients who respond fully to pyridoxine (with normalization or near normalization of urine oxalate) can do well, as can those with PH2, but otherwise the new kidney is at significant risk from oxalate deposition and rapid failure, particularly if there is delayed graft function. Liver transplantation The rationale for liver transplantation relies on the fact that AGT is more or less liver specific and, although GRHPR is more widely dis- tributed, its activity in the liver greatly exceeds that in other tissues. Liver replacement thus has the potential to replace all, or almost all, the body's requirement for AGT and, to a lesser extent, GRHPR. Several hundred liver transplantations, often combined with kidney transplantation, have been carried out worldwide for PH1 resulting in a metabolic cure, although it may take many years for the urinary excretion of oxalate to be normalized. This is especially the case if patients have spent many years with poor renal function or on haemodialysis, during which time the corporeal load of calcium ox- alate has built up, particularly in the bones. Pre-emptive liver transplantation before the GFR has decreased to 30 ml/min per 1.73 m2 is an option to be considered if PH1 is diag- nosed early and is following an aggressive course. The risks of the transplant procedure, the added years of immunosuppression, and the difficulty in accurate prediction of rate of loss of renal function must be balanced against the benefit. Heterotopic auxiliary liver transplantation is theoretically unsound since the remaining native liver continues to make large amounts of oxalate. Liver transplant- ation has been shown to reduce oxalate excretion to normal in a single PH2 patient who had progressed to end stage kidney disease (Dhondup et al. 2018). Further experience will be needed to evaluate its role in management of PH2. Timing of renal replacement therapy/transplantation Initiation of maintenance dialysis or transplantation should be ac- complished as soon as the plasma oxalate concentration begins to exceed the solubility threshold for calcium oxalate. This occurs in most patients at a GFR of 20 to 25 ml/min per 1.73 m2, though can occur earlier in some cases. The purpose of early initiation of renal replacement therapy is to minimize systemic oxalosis and reduce the risk of calcium oxalate deposits in any subsequently grafted kidney. Indeed, it has been suggested that PH1 patients who are either un- responsive or only partially responsive to pyridoxine should be managed with pre-emptive (before dialysis is required) combined liver and kidney transplantation. By contrast, PH1 patients who re- spond fully to pyridoxine, with normalization or near normalization of urine oxalate while on treatment, and patients with PH2, can do well with kidney transplantation alone. Any time from initiation of dialysis to transplantation should be kept as short as possible to min- imize systemic oxalate accumulation. Vigorous dialysis, required daily in most patients, is needed. The plasma oxalate concentration and urine oxalate excretion rate should be followed sequentially before and after transplantation until normal. Elimination of tissue oxalate stores can take up to 3 years or more following successful transplantation. Careful man- agement of hyperoxaluria throughout this time is essential to avoid damage to the renal allograft. Future developments A recent avenue of research is based on

substrate reduction, which has the potential to be applicable to more PH types and mutations. The aims are either to reduce the amount of glyoxylate produced, since it is the precursor to oxalate, or decrease its oxidation to oxalate. The inhibition of the enzyme glycolate oxidase is targeting the peroxi- somal source of glyoxylate. Inhibition of the enzyme hydroxyproline oxidase targets the mitochondrial source of glyoxylate. Inhibition of the enzyme lactate dehydrogenase targets the oxidation of glyoxylate to oxalate, the last step, common to all PH types. These new thera- peutic strategies rely on small interfering RNA (siRNA) administra- tion or use the CRISPR/Cas9 technology. Other more conventional strategies aim at identifying drugs capable of such enzyme inhib- itions. Recent work on calcium oxalate mediated kidney inflamma- tion suggest a potential adjunct role for targeting the inflammatory reaction to preserve renal function. Following promising work in

 animal models of PH1, clinical trials of siRNA therapeutics are cur- rently underway (phase II/III) and show great promise. Just as the discovery of AGT deficiency in PH1 heralded the introduction of enzyme replacement therapy by liver transplantation 30 years ago, so recent discoveries on the functional relationships between mu- tations and enzyme dysfunction will lead to the design of pharma- cological countermeasures. Mutation-specific chemical chaperones have potential as future treatments for patients with PH1 or PH2 who have missense mutations in AGT or GRHPR. Several screening procedures have been developed to identify chemical chaperones in panels of repurposed pharmaceutical drugs. Gene therapy for PH was forecast more than 15 years ago. Hepatocyte transplantation in an AGT knockout mouse model has been attempted, but this technique requires suppression of the host hepatocytes. Adeno-associated virus gene transfer has also been attempted in mice but requires further improvements. A re- cent study has identified a drug that can decrease the mitochon- drial mistargeting of AGT seen with certain mutations. Continued research in that direction may yield more candidates. Probiotics such as the oxalate-degrading bacteria Oxalobacter for- migenes have been the subject of interest for a few years, but have not proven their efficacy in human clinical studies for PH so far, despite their potential to increase oxalate gut secretion. Multiple novel avenues for treatment of PH are explored and offer new hope for patients with this rare disease. FURTHER READING Anders HJ, et al. (2018). The macrophage phenotype and inflammasome component NLRP3 contributes to nephrocalcinosis-related chronic kidney disease independent from IL-1-mediated tissue injury. Kidney Int, 93(3), 656–69. Belostotsky R, et al. (2010). Mutations in DHDPSL are responsible for primary hyperoxaluria type III. Am J Hum Genet, 87, 392–9. Cochat P, et al. (2012). Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. Nephrol Dial Transplant, 27, 1729–36. Cramer SD, et al. (1999). The gene encoding hydroxypyruvate reduc- tase (GRHPR) is mutated in patients with primary hyperoxaluria type II. Hum Mol Genet, 8, 2063–9. Danpure CJ, Jennings PR (1986). Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. FEBS Lett, 201, 20–4. Dhondup T, et al. (2018). Combined liver-kidney transplantation for primary hyperoxaluria type 2: A case report. American Journal of Transplantation, 18(1), 253–7. Dutta C, et al. (2016). Inhibition of glycolate oxidase with dicer-substrate siRNA reduces calcium oxalate deposition in a mouse model of primary hyperoxaluria type 1. Mol Ther, 24, 770–8. Hopp K, et al. (2015). Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria. JASN, 26, 2559–70. Hoppe B, et al. (2009). The primary hyperoxalurias. Kidney Int, 75, 1264–71. Liebow A, et al. (2017). An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. J Am Soc Nephrol, 28(2), 494–503. Mandrile G, et al. (2014). Outcome of primary

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