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The primary hyperoxalurias

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The primary hyperoxalurias (PHs) are rare disorders of glyoxylate metabolism in which specific hepatic enzyme deficiencies result in overproduction of oxalate. Due to the resulting severe hyperoxaluria, recurrent urolithiasis or progressive nephrocalcinosis are principal manifestations. End stage renal failure frequently occurs and is followed by systemic oxalate deposition along with its devastating effects. Due to the lack of familiarity with PHs and their heterogeneous clinical expressions, the diagnosis is often delayed until there is advanced disease. In recent years, improvements in medical management have been associated with better patient outcomes. Although there are several therapeutic options that can help prevent early kidney failure, the only curative treatment to date is combined liver–kidney transplantation in patients with type I PH. Promising areas of investigation are being identified. Knowledge of the spectrum of disease expression, early diagnosis, and initiation of treatment before renal failure are essential to realize a benefit for patients.

Kidney International (2009) **75,** 1264–1271; doi:10.1038/ki.2009.32; published online 18 February 2009

KEYWORDS: nephrocalcinosis; oxalate; systemic oxalosis; urolithiasis

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Received 24 November 2008; revised 5 January 2009; accepted 13 January 2009; published online 18 February 2009

Primary hyperoxaluria (PH) type I and type II are relatively rare autosomal recessive inborn errors of glyoxylate metabolism, which result in markedly increased endogenous oxalate synthesis by the liver, and to a minor degree in PH II by other body cells. Type I primary hyperoxaluria (MIM 604285) is caused by deficient or absent activity of liver-specific peroxisomal alanine/glyoxylate aminotransferase (AGT[1]). In some patients with PH type I enzyme is present but mistargeted to mitochondria where it is metabolically inactive. Primary hyperoxaluria type II is a somewhat milder but not benign variant (PHII, MIM 260000, 604296) that occurs as a result of deficient glyoxylate reductase/hydroxypyruvate reductase (GRHPR) enzyme activity.[2] A small number of patients have been described with a phenotype similar to that of PH I and PH II but with normal AGT and GRHPR enzyme activities. The specific etiology of the hyperoxaluria in such patients remains to be elucidated and they are referred to as non-I, non-II PH patients.[3]

Among disorders causing hyperoxaluria, the PH are the most severe, ultimately leading to end-stage renal failure (ESRF) and if untreated, death in most of the patients.[4] PH (endogenous) must be differentiated from the more common secondary forms. In secondary hyperoxaluria, there is either dietary or other exposure to large amounts of oxalate or oxalate precursors or there is an underlying disorder that causes increased absorption of (dietary) oxalic acid from the intestinal tract. The latter is usually characterized by fat malabsorption. Among secondary causes of hyperoxaluria, those attributable to gastrointestinal (GI) disease (for example, inflammatory bowel diseases, cystic fibrosis, status post-bariatric surgery, short bowel syndrome (SBS)) can lead to severe hyperoxaluria due to enhanced absorption of oxalate from the GI tract and may result in reduced renal function. Most other forms of absorptive secondary hyperoxaluria are of milder degree (0.55 to <0.8 mmol/1.73 m^2 per day) and usually carry a better prognosis. In contrast to inflammatory bowel diseases or short bowel syndrome patients with PH show oxalate absorption within normal limits ($<15\%$).[5]

Oxalate cannot be metabolized in mammals and is primarily eliminated through the kidneys as an end product of metabolism. Oxalate is freely filtered at the glomerulus and also secreted by the tubules. In all types of PH, very high urinary oxalate excretion, typically >1 mmol/1.73 m^2 per day

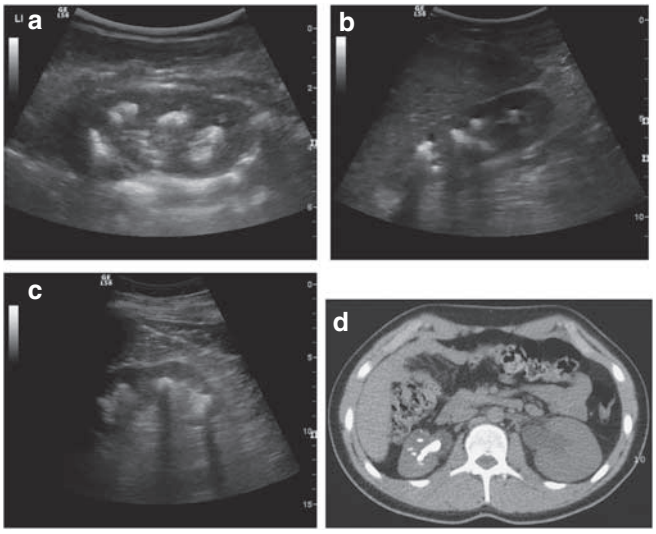

Figure 1 | Radiographic findings in PH. (**a-c**) Typical sonographical and X-ray findings of severe urolithiasis in patients with primary hyperoxaluria (PH) type I aged 5, 9, and 39 years and with still normal or only slightly impaired renal function. (**d**) Low enhanced computed tomography scan showing a Staghorn calculus and five further smaller stones in the right kidney of a 16-year-old patient with PH, uncompliant with regard to medication and fluid intake.

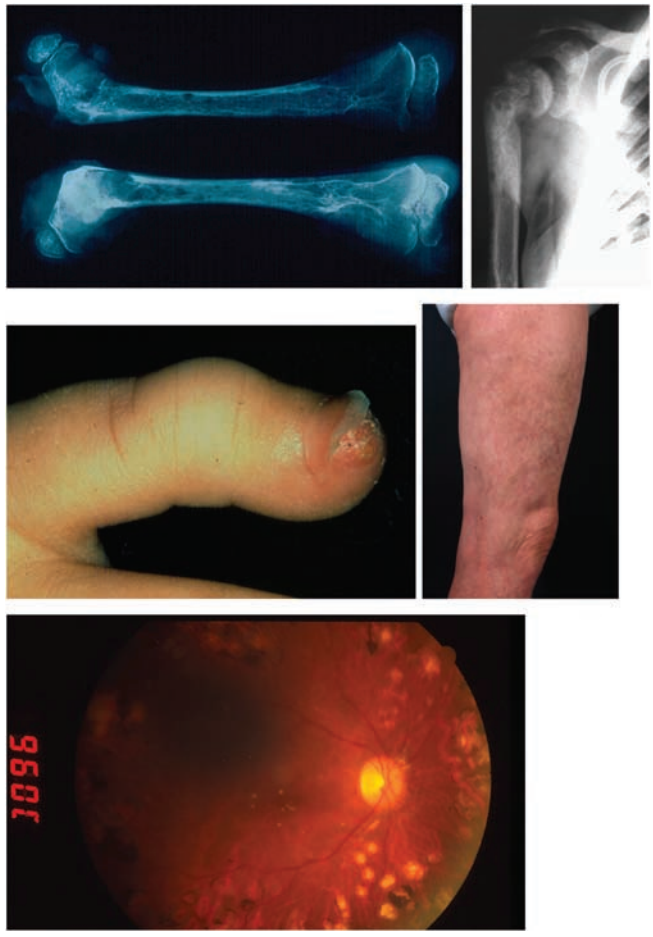

Figure 2 | Severe systemic oxalosis—calcium oxalate depositions in the bone (osteolytic lesions, epiphyseolysis), skin (crystal deposition at finger tip, livedo reticularis-like picture) and retina in different patients with primary hyperoxaluria type I.

(normal <0.5), is observed. The urine becomes supersaturated for calcium oxalate resulting in formation of complexes and crystals within the tubular lumen. The crystals attach to the surface of renal tubular cells, allowing aggregation of crystals into stones (urolithiasis), others are incorporated into the renal tubule cells, and some further migrate into the renal interstitium (nephrocalcinosis), the clinical hallmarks of the PH (Figure 1). Progressive renal parenchymal inflammation and interstitial fibrosis from progressive nephrocalcinosis and recurrent urolithiasis along with secondary complications (urinary tract infection, obstruction) cause renal impairment, which progresses to ESRF over time.[6–8] Once renal function declines to a glomerular filtration rate (GFR) below 30–40 ml/min per 1.73 m^2 body surface area, renal excretion of oxalate is sufficiently compromised that plasma oxalate concentration rises (normal limits 1–6 µmol/l[9]) and can rapidly exceed the supersaturation threshold for calcium oxalate as levels >30 µmol/l are reached. Systemic deposition of calcium oxalate (oxalosis) then occurs in extra-renal tissues, including retina, myocardium, vessel walls, skin, bone, and the central nervous system among others (Figure 2). Long-term consequences include cardiomyopathy, cardiac conduction disturbances, vasculopathy, heart block, treatment-resistant anemia, oxalate osteopathy resulting in debilitating bone and joint pain, retinopathy and if untreated, early death.[4,10] Thus, the hepatic defect, which primarily manifests within the urogenital tract, when advanced, becomes a devastating multisystemic disorder. Owing to the risk of systemic oxalosis, renal replacement with dialysis or transplantation is required earlier in patients with PH than those with renal insufficiency from other causes. Yet, the systemic nature of the clinical manifestations may obscure the diagnosis for years. Awareness of PH as a possible cause and measurement of plasma as well as urinary oxalate are essential initial steps.[7]

Owing to the nature of the metabolic defects in PH, marked hyperoxaluria is present from birth, yet there is marked heterogeneity of disease expression. Severe 'infantile oxalosis' with early ESRF in PH type I occurs in some patients, whereas others lack clinically apparent sequela well into adulthood.[4] Although PH are considered rare with a prevalence of 0.8–2.9 per 10^6 populations and an estimated incidence rate of 0.1–0.2 per 10^6 populations, they appear to be under diagnosed. This is suggested by the high proportion of patients (up to 35%) in whom diagnosis is made only after advanced renal failure has developed or, even worse, after early kidney graft failure from recurrent oxalosis following isolated kidney transplantation.[6–8]

Early diagnosis, molecular subtyping, and prompt initiation of treatment are of vital importance for PH patients. This is best illustrated by recent clinical studies showing improved outcome with median age at ESRF being now >30