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Review

The primary hyperoxalurias: A practical approach to diagnosis and treatment

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HIGHLIGHTS

- Calcium oxalate urolithiasis is common.
- Primary hyperoxaluria (PH) must be excluded in all patients presenting with calcium oxalate urolithiasis.
- Phenotypic variability in PH may delay a diagnosis.
- PH is an important cause of renal failure.
- Understanding phenotype/genotype correlations directs treatment and assists predictions for decline in renal function.

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ABSTRACT

Although the primary hyperoxalurias (PH) are rare disorders, they are of considerable clinical importance in relation to calcium oxalate urolithiasis and as a cause of renal failure worldwide. Three distinct disorders have been described at the molecular level. The investigation of any child or adult presenting with urinary tract stones or nephrocalcinosis, must exclude PH as an underlying cause. This paper provides a practical approach to the investigation and diagnosis of PH, indicating the importance of distinguishing between the PH types for the purposes of targeting appropriate therapy. Conservative management is explored and the various transplant options are discussed.

The primary hyperoxalurias are inborn errors of metabolism of which three have been described at the molecular level. Primary hyperoxaluria type 1 (PH1) results from mutations in the *AGXT* gene with associated dysfunction of the vitamin B6 (pyridoxine) dependent liver specific peroxisomal enzyme alanine: glyoxylate aminotransferase (AGT) [1]. Primary hyperoxaluria type 2 (PH2) arises from mutations in the *GRHPR* gene with subsequent dysfunction of the enzyme glyoxalate/hydroxypyruvate reductase (GRHPR) [2]. Primary hyperoxaluria type 3 (PH3) arises from mutations in the *HOGA1* gene which encodes the mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase [3] (see Fig. 1).

Although the primary hyperoxalurias are rare disorders, they are of considerable clinical importance in that they account for approximately 2% of patients starting renal replacement therapy before the age of 15 in European and North American surveys; and in countries where the frequency of parental consanguinity is high, such as Tunisia, are responsible for 17% of children with chronic renal failure [4–6]. Primary hyperoxaluria accounts for 7–14% of children with nephrocalcinosis [7].

Oxalate is derived principally from the diet and endogenous production following the metabolism of glyoxylate and ascorbic acid. Excretion is primarily via the kidney. The majority of patients presenting with hyperoxaluria do so as a result of derangement of the normal metabolic pathways. Hyperoxaluria can occur due to hyperabsorption of ingested oxalate, as seen in patients with bowel malabsorption e.g. ulcerative colitis or Crohn's disease, through altered fatty acid absorption.

As oxalate is poorly soluble, calcium oxalate calculi will form when the urine becomes supersaturated. Bidirectional transport of oxalate has been demonstrated in proximal renal tubular cells and in intestinal epithelia, with evidence to suggest a role for the *SLC26A6* gene in both enteric and renal oxalate transport. Calcium

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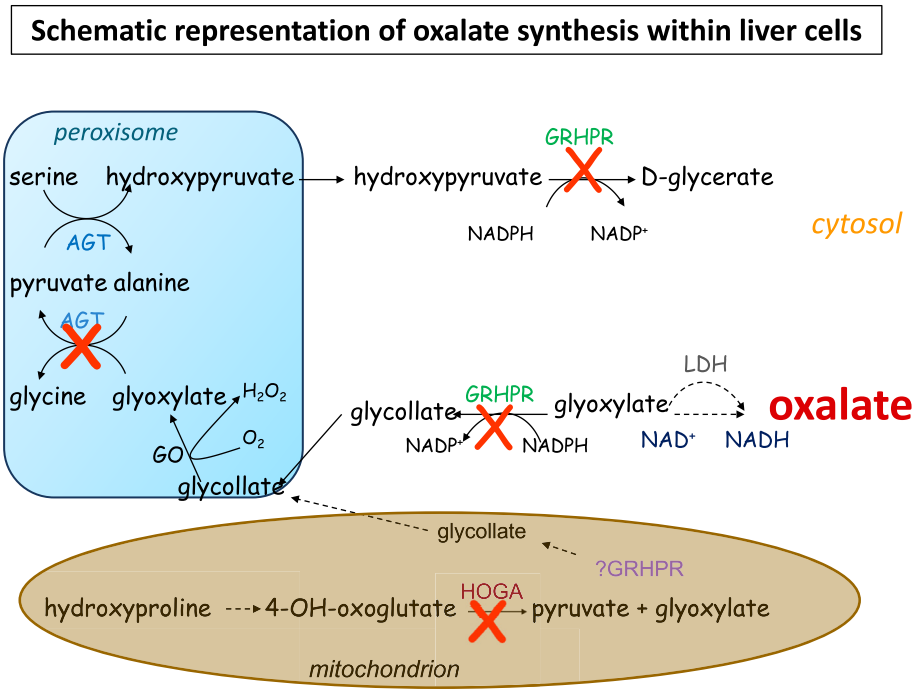

Fig. 1. Schematic representation of oxalate synthesis within liver cells.

oxalate crystals form in the lumen of the renal tubules, where the crystals adhere to the tubular epithelium, are internalised into the cells, with subsequent extrusion into the interstitial region where they cause an inflammatory reaction and nephrocalcinosis [8].

1. Presentation and investigation

The primary hyperoxalurias show considerable genetic and phenotypic heterogeneity, presenting in the following forms:

- Asymptomatic
- Occasional passage of renal stones
- Recurrent urolithiasis
- Recurrent urolithiasis with the development of nephrocalcinosis and eventual progressive renal failure
- Infantile presentation with faltering growth, early nephrocalcinosis and rapid progression to end stage renal failure

Although the majority of patients present with renal calculi in childhood the clinical presentation can range from death in infancy in PH1 to asymptomatic cases in adulthood [9]. This phenotypic diversity, together with the rarity of the disease may account for the delay in diagnosis commonly noted in these patients. End stage kidney disease is the presenting feature in 20–59% depending on the population group, with diagnosis clarified in some after failed kidney transplant [4,10]. Approximately 10% of asymptomatic patients are identified through family screening.

Even within the same family variable phenotypes are noted, ranging from asymptomatic urinary oxalate excretion to early onset end stage renal disease [11,12]. It is possible that differences in genetic background or epigenetic factors can produce milder expressions of disease as noted in the Japanese population [13]. Understanding phenotype/genotype correlations will assist predictions for decline in function [14].

The investigation of any child or adult presenting with even the occasional passage of renal stones, but certainly for those presenting with nephrocalcinosis, must exclude PH as an underlying cause. In all such presentations a **fresh** urine sample must be sent for urine oxalate/creatinine ratio in the first instance, consulting age related tables as ratios in early life are influenced by prematurity and nutrition [15,16]. If the sample is borderline or elevated, a 24 h urine collection for oxalate excretion is required, and in some cases, three consecutive 24 h urine collections, as there is marked variability in the excretion of oxalate on a day to day basis. During the 24 h collection period the urine collection must be placed into an acidified container (usually hydrochloric acid prepared by the clinical chemistry laboratory). The plasma oxalate level may not be raised unless there is considerable nephrocalcinosis or a decline in the glomerular filtration rate (GFR) has occurred. Note that patients with end stage renal failure of any cause demonstrate a raised plasma oxalate due to inadequate excretion. Normal urinary oxalate excretion has been noted in children with reduced GFR <30 mls/min1/.73 m^2 so caution is required in this group [17]. Some untreated patients with PH1 in family studies may have a normal urinary oxalate or only slightly elevated excretion (0.5–1.0 mmol/24 h/1.73 m^2) [18]. Blood and urine samples collected for oxalate analysis must be sent immediately to the laboratory as any delay can result in a false elevation of the oxalate levels. In addition, patients must not be taking any form of vitamin C supplements as ascorbic acid ingestion will elevate urinary oxalate.

A urine oxalate (UOx) excretion of >0.5 mmol/1.73 m^2/day is likely to be due to a metabolic cause although some secondary cases due to Crohn's disease, short gut syndrome and pancreatic insufficiency have grossly elevated oxalate excretions >1 mmol/1.73 m^2/day. Urinary glycolate excretion may be raised in PH1 and PH3 so has a low diagnostic sensitivity and specificity [3].

Patients presenting with renal stones and/or nephrocalcinosis must also have the urine analysed for L-glyceric acid (part of a routine organic acid screen) as the hallmark of **PH2** is a high excretion of L-glyceric acid >28 mmol/mol of creatinine. It is impossible to differentiate clinically between PH types 1 and 2, thus