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What is *new* in primary hyperoxaluria?

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Introduction

Although the majority of renal stones both in children and in adults are formed by calcium oxalate (CaOx), few patients actually suffer from a *primary* metabolic defect leading to excessive endogenous production of oxalate. Nevertheless, there is considerable interest in primary hyperoxaluria (PH)—the prototype and model of hyperoxaluria—since a better understanding of the pathogenic mechanisms is also expected to help the much larger group of patients with urolithiasis not suffering from PH. Two recent symposia (NIH Workshop, 8–9 December 1998, Bethesda, USA and 5th Workshop on PH, 12–13 March 1999, Zurich,

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Switzerland) have dealt with these problems [1]. It has become obvious that PH is a highly complex disorder, consisting of two well-described forms (PH1 and PH2) and of further conditions.

Toxicity

Oxalate is a useless end-product of metabolism and is normally completely excreted by the kidneys (normal excretion <0.5 mmol (45 mg)/24 h/1.73 m^2). Oxalate and calcium oxalate (CaOx) crystals, once believed to be biologically inert, exert toxic effects on renal epithelial cells [1 (A 11,12); 2–4]. These effects are comparable to those resulting from oxidative stress on tissues, because oxalate increases the production of free radicals [2]. The extremely high urinary oxalate concentrations in patients with PH may therefore be harmful. Thus, any increase in oxalate not only has a strong effect on the urinary saturation of CaOx (10 times as much as an equimolar increase of calcium), but in addition may lead to *direct* tubular damage.

Intestinal absorption

Only 5–10% of the urinary oxalate normally originates from daily nutrition. This fraction is even lower in PH patients, considering their extremely high endogenous oxalate production. However, intestinal absorption might become a relevant factor if it is increased (as is the case in some forms of secondary hyperoxaluria). Absence of the anaerobic intestinal oxalate-degrading bacterium *Oxalobacter formigenes* (which is found in up to 80% of the normal population) has been shown to be associated with (secondary) hyperoxaluria in patients with cystic fibrosis and in patients with recurrent urolithiasis [1 (A 16); 5]. Another cause of increased intestinal oxalate absorption is calcium restriction, as less calcium is available to bind oxalate and to form (insoluble) CaOx complexes in the gut.

Plasma oxalate and CaOx saturation

Plasma oxalate (P_{Ox}) and plasma CaOx saturation (β_{CaOx}) are increased early in PH patients [6,7]. Therefore the main purpose of therapy is to lower P_{Ox} and β_{CaOx} (to which P_{Ox} is significantly correlated) or at least to prevent its steady increase. Both parameters are inversely correlated with GFR, hence the risk of systemic CaOx deposition (oxalosis) is increased in renal insufficiency, even before end-stage renal failure (ESRF) occurs [6].

Liver biopsy

Urinary metabolites often are not conclusive for diagnosis of PH1 or PH2. The enzyme defects of PH1 and PH2 can now be determined in hepatic tissue from the same core obtained by needle biopsy [1 (A 9); 8]. Precise diagnosis is of great importance for prognosis (type of PH), genetic counselling including prenatal diagnosis, and if liver transplantation is considered.

Primary hyperoxalurias

PH1

PH1—a 'nephrological liver disease'—is due to a defect or absence of liver-specific peroxisomal alanine:glyoxylate aminotransferase (AGT), resulting in elevated urinary excretion of oxalate and (in most cases) of glycolate. The AGXT gene is located on chromosome 2q37.3 and spans over 11 exons [9]. Over 25 different mutations have been found so far. Around 30% of patients have the $G_{630}A$ mutation, leading to a $Gly_{170}A$ amino acid substitution, which is mostly associated with a $C_{154}T$ polymorphism ($Pro_{11}Leu$). This mutation is particularly interesting because it leads to an unparalleled protein trafficking defect in which AGT is mistargeted from peroxisomes to mitochondria. Further studies have yielded insights into some of the fundamental differences in the way proteins are targeted to, and imported into, peroxisomes and mitochondria [9].

Clinically, PH1 is also very heterogeneous, with the spectrum ranging from early ESRF (infantile oxalosis) to occasional kidney stones in adults [1]. The clinical heterogeneity is not sufficiently explained, neither by AGT activity or localization, nor by disease specific genotypes. Even siblings with an identical mutation may have a completely different course of the disease [10].

Diagnosis of PH1 is still being missed or delayed all too often, and figures reported represent a minimum. Data from the UK, Switzerland and France suggest that 1 in 60 000 to 120 000 children suffers from PH1 [1 (A 2); 11]. The disease is far more common in certain countries like Tunisia, where PH1 is the cause of ESRF in 13% of paediatric patients as compared to 0.3% in Europe [1 (A 3,4)]. From Israel, seven distinct mutations (including five novel ones) were reported in eight heavily inbred (Israeli–Arab) families with a high prevalence of the severe infantile form [1 (A 5)].

Therapy of PH1

Generous fluid intake and administration of potassium citrate or phosphate together with pyridoxine (vitamin B_6) is still the basis of therapy. Attempts to reduce the glyoxalate or glycolate pool have not yet been successful [1 (A 14)]. There was agreement to define pyridoxine responsiveness as $>30\%$ reduction of urinary oxalate excretion from baseline after stepwise increase of daily dosage of pyridoxine (5–10–15–20 mg/kg after several weeks) [1 (A 15)].

Transplantation

According to the latest European Oxalosis Registry Report, actuarial patient survival (98 grafts in 93

patients) is 80% at 6 years for combined liver/kidney transplantation (with a much poorer outcome for patients <5 years of age) [1 (A 19)]. This treatment modality is at present the method of choice for PH1 patients in ESRF. Isolated kidney transplantation, advocated in the USA [1 (A 21)], may still be an alternative, e.g. in B_6-responsive patients [7]. No such therapy is available in some developing countries having a high incidence of PH1. Dialysis is no alternative except for a very limited time.

Why not perform pre-emptive (isolated) liver transplantation [1 (A 22, 11)]? Thus far, some 10 patients with PH1 not in renal failure have been treated this way with reasonable results. However, some of the patients might have maintained their renal function without intervention. It is impossible to establish guidelines, and it seems unlikely that pre-emptive liver transplantation will become popular in PH1.

Prospects of gene therapy

Considerable problems need to be overcome. In analogy to auxiliary liver transplantation (which does not work because the diseased liver will continue to produce oxalate in excess), it would require far more than 20 or 30% of liver cells to be transfected—a task impossible to solve with current vector technology [1 (A 1)]. However, the goal is set.

PH2

PH2 results from absent glyoxylate reductase (GR) activity (GR also possesses hydroxypyruvate reductase and D-glycerate dehydrogenase activity). Much progress has been made in this disease which primarily leads to repeated stone formation and less to nephrocalcinosis and ESRF. The hallmark is the high urinary excretion of oxalate and L-glyceric acid. Diagnosis can now be confirmed by measurement of GR activity in liver biopsy [1 (A 9); 8]. The responsible gene has been mapped to the centromeric region of chromosome 9 (probably p11) and contains nine exons [1 (A 7; 12)]. PCR-SSCP and sequence analysis of DNA from four patients of three different families have identified a single nucleotide deletion in exon 2 resulting in a frameshift mutation [1 (A 7)].

PH2 is also underdiagnosed; one-third of paediatric patients with PH in the West Midlands (UK) turned out to have PH2 and not PH1 [1 (A 2)].

Atypical PH

As it has been the case in other metabolic diseases, the advent of enzyme measurement has demonstrated clearly that PH is heterogeneous: not all patients with PH (i.e. without evidence of secondary hyperoxaluria) can be classified as PH1 or PH2. These patients, observed at different places, had early manifestation of urolithiasis [1 (A 17,18)]. Why not call this condition PH3? There is considerable evidence that this group is heterogeneous and contains further subtypes (PH4, etc.). The search for the metabolic defect(s) in atypical PH, the term preferred at the Workshop, is ongoing.

Conclusion

In conclusion, much progress has been made during recent years, and molecular genetics and enzyme diagnostics have firmly been established in PH1 and PH2. However, considerable effort is necessary to explain the discrepancy between genotype and phenotype in PH1 and to define the underlying metabolic defects of atypical PH. The optimal treatment, especially for patients with PH1 and renal insufficiency remains a matter of debate, and not all agree with early enzyme replacement therapy = pre-emptive liver transplantation. Intensified research in PH will also benefit the large number of patients with secondary hyperoxalurias. No doubt, the 6th PH workshop will be exciting again!

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Editor's note

Please see also the Fifth Workshop on Primary Hyperoxaluria Abstracts (pp. 2784–2789 in this issue).