The third workshop on primary hyperoxaluria

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The phenotypic expression of primary hyperoxaluria type I (PH1) varies widely and although the disease classically presents in childhood with aggressive stone disease and marked hyperoxaluria, some patients have relatively mild stone disease of late onset in the presence of marked hyperoxaluria, while others have only mild hyperoxaluria but aggressive stone disease. This stems from the genetic variation in relation to the PH1 gene itself, the overall genetic and metabolic background against which mutations of the alanine:glyoxylate aminotransferase (AGT) gene are expressed, the patient's long-term state of hydration, and the excretion of the urinary constituents that influence stone formation in general [1,2].

The urinary oxalate concentration is, after the urinary volume, the most important urinary risk factor for idiopathic calcium oxalate stone formation [3] and it is tempting to speculate on the extent to which mutations in the AGT gene, producing relatively small increases in the rate of oxalate synthesis, may be a factor in the genesis of this common condition. Progress in this area would require liver biopsies for AGT assays and immunocytochemical localization studies as well as sequential blood and urine oxalate measurements. The analysis of genomic DNA for specific mutations may, when their full range is known, offer a more clinically acceptable approach.

The gene directing the synthesis of AGT has the assignment 2q36-37. It has been cloned [4] and the usual types of mis-sense and non-sense mutations have been reported. About 30% of PHI patients have residual catalytic activity, and in these individuals the mutation alters the quaternary structure and properties of the AGT molecule in such a way that it migrates from its site of synthesis on the rough endoplasmic reticulum to mitochondria instead of to peroxisomes. The other peroxisomal enzymes are not mislocated. This is a unique type of metabolic lesion and its discovery has brought basic knowledge of the mitochondrial and peroxisomal targeting of proteins into the clinical arena.

Some patients are now referred for treatment earlier in the clinical evolution of their disease than formerly, and before they are grossly oxalotic. This, together with the ability to identify patients with an appreciable amount of residual AGT catalytic activity, makes it appropriate to reappraise the relative merits of combined hepatorenal transplantation and either liver or kidney transplantation alone. Combined hepatorenal transplantation is the procedure of choice for patients who present late with systemic oxalosis. It is essential for the diagnosis to have been proved enzymologically on a liver biopsy before liver transplantation.

The position may be different in the case of patients with appreciable residual catalytic activity. Here, the plasma oxalate may remain well below the concentration at which the plasma becomes supersaturated with calcium oxalate [5] and there may be little systemic oxalosis even when renal function is virtually zero and the patient is being treated by a dialysis regime that removes oxalate relatively inefficiently. Here, a renal graft, with any stones forming in the graft being promptly treated by extracorporeal shockwave lithotripsy, may be appropriate. Conversely, patients with zero or minimal residual AGT activity but well-preserved renal function can be considered for a regime based on stone treatment by extracorporeal shockwave lithotripsy and endoscopic procedures with an orthotopic liver graft to correct oxalate overproduction and thereby preserve renal function. The selection of patients for these different treatments will depend on careful appraisal of their clinical state with particular reference to the degree of oxalosis and renal damage, and on the results of liver AGT assays together with the results of sequential plasma and urinary oxalate excretion levels. The extent to which the judicious use of modern techniques for stone disruption and the endoscopic extraction of stone fragments can delay the need for transplantation requires further study. If the patient still has appreciable renal function (GFR > 20–25 ml/min/1.73 m2) or is to be treated by renal transplantation only, the effect of pharmacological doses of pyridoxine on oxalate production should be assessed.

Liver transplantation for the treatment of PH1 is both gene and enzyme replacement therapy. Other approaches to gene therapy merit consideration. The ex vivo method in which the patient's hepatocytes, obtained by partial hepatectomy, are transfected with a recombinant retrovirus carrying the wild-type gene...
and reintroduced into the liver by embolization through the inferior mesenteric vein has produced partial biochemical correction in LDL receptor deficiency (familial hypercholesterolaemia) [6]. This approach might be applicable to PHI. The more speculative in vivo approach would be to use a systemically administered modified hepatotropic virus to carry the normal gene into the patient’s hepatocytes, as has been suggested for neurones using the herpes simplex virus HSV-1 [7].

Neither liposome carriage nor receptor-mediated endocytosis appear suitable for the enzyme replacement in PHI because AGT is peroxisomal and not a lysosomal enzyme.

The clinical phenotype of primary hyperoxaluria type 2 [glyoxylate reductase (d-glycerate dehydrogenase) deficiency] is identical with that of PHI. The general measures, hydration, the administration of magnesium ions, citrate ions, orthophosphate and the vigorous application of modern stone disruption and nephroscopic procedures, apply to its treatment. However, the metabolic lesion in PH2 is more widely distributed than that in PHI. Thus, the extent to which either liver transplantation or liver-directed enzyme or gene replacement therapy may be of value will depend inter alia on the proportion of the whole-body glyoxylate reductase activity that is located in the liver. Glyoxylate reductase is expressed in leucocytes and bone marrow transplantation might be considered as a definitive therapy.

References

2. Watts RWE. Primary hyperoxaluria type 1. Q J Med 1994; 87: 593–600