

CURRENT TOPIC

Current approaches to the management of primary hyperoxaluria

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Primary hyperoxalurias (PH) are very rare diseases characterised by overproduction and accumulation of oxalate in the body. The main target organ is the kidney, as oxalate cannot be metabolised and is excreted in the urine, leading to nephrocalcinosis, recurrent urolithiasis, and subsequent renal impairment. During the last decade, major advances in enzymology, molecular genetics, and cell biology have generated excellent reviews on both pathophysiology and management^{1 2}; however, specific questions remain unanswered.

Urinary oxalate

Basically, hyperoxaluria (normal urinary oxalate < 0.5 mmol/1.73 m² per day; normal urinary oxalate to creatinine ratio < 0.10 mmol/mmol) and calcium oxalate crystallisation are the hallmarks of any kind of PH.¹ The presence of monohydrated calcium oxalate crystals in the urine or tissues can be assessed by infrared spectrometry or polarised light microscopy.³ Hyperoxaluria may be associated with increased urinary excretion of either glycolate in PH1 or L-glycerate in PH2, but urinary metabolites are no longer adequate for accurate diagnosis, which requires either enzyme assessment or DNA analysis.^{4 5}

Primary hyperoxaluria type 1 (PH1)

GENETICS

PH1 is an autosomal recessive disorder of glyoxylate metabolism (1 in 120 000 live births in France)⁶ caused by deficiency of the hepatic peroxisomal pyridoxal phosphate dependent enzyme alanine-glyoxylate aminotransferase (AGT), the gene of which, *AGXT* (about 10 kb), has been sequenced and located on chromosome 2q37.3.² Over 25 mutations have been identified so far, but most of them are solitary mutations, and only 25% of the patients have both alleles identified. So far, no mutation at all has been found in one third of the patients. The most common mutations (G170R and I244T) are encountered in 40% of alleles, so their identification may lead to direct diagnosis in selected populations (O Basmaison 1999, personal communication).^{7 8} The disease occurs either because AGT activity is undetectable (two thirds) or because it is mistargeted to mitochondria (one third), leading to considerable clinical and enzymic heterogeneity.^{1 2 9}

A POOR PROGNOSIS

Independent of its molecular pattern, PH1 grossly fits three clinical presentations: (a) a rare infantile form with early nephrocalcinosis and rapid kidney failure; (b) a rare late onset form with occasional stone passage in late adulthood; (c) the most common form with recurrent urolithiasis and progressive renal failure leading to a diagnosis of PH1 in childhood or adolescence.⁵ With advancing renal failure, patients experience progressive systemic involvement (bone, joints, retina, heart, vessels, nerves) which is responsible for a poor quality of life leading to both disability and life threatening complications.^{1 5} Half of all patients reach end stage renal disease (ESRD) before 25 years of age; PH1 is responsible for less than 0.5% of ESRD in children in Europe compared with 13% in Tunisia, which is due to frequent consanguinity.^{6 10} Such an outcome strongly argues for pre-emptive transplantation in patients with severe pyridoxine unresponsive PH1.

PLEA FOR EARLY AGGRESSIVE CONSERVATIVE TREATMENT

Treatment, including high fluid intake and administration of calcium oxalate crystallisation inhibitor and pyridoxine, should be started as soon as a diagnosis of PH1 has been made. It should also be given to any neonate or family member of an index case until the diagnosis is completed/excluded. When urinary oxalate exceeds 0.4 mmol/l, the risk of stone formation is increased, especially if urinary calcium exceeds 4 mmol/l; therefore supportive treatment should be adopted to keep the concentration of oxalate and calcium below these limits. This can be achieved by a high fluid intake (> 2 litres/m² per day) supplemented with calcium oxalate crystallisation inhibitors—for example, potassium (and/or sodium) citrate (100–150 mg/kg per day).^{11 12} Diuretics require careful management, as frusemide is able to maintain a high urine output but there is a risk of increased calciuria, whereas the diuretic effect of hydrochlorothiazide is less pronounced but is associated with an appreciable decrease in calcium excretion; a combination of the two would help to reduce urinary calcium.¹² Restriction of dietary oxalate intake has very limited effect on the disease.¹ Pyridoxine sensitivity is found in 10–40% of patients, so such

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treatment must be tried early at a daily dose of 3–5 mg/kg, with stepwise increases to 15 mg/kg.⁷ Response to pyridoxine may delay the progression to ESRD; it can be detected by measurement of both oxalate and glycolate and should be tested at all stages of the disease.¹³ Specific pharmacological agents—for example, procysteine—have limited effects and are unable to lower urinary excretion of oxalate appreciably. The effect of any conservative measures should be assessed by serial determination of the crystalluria score and calcium oxalate supersaturation.^{14 15}

DIALYSIS TREATMENT

Conventional dialysis is unsuitable for PH1 patients who have reached ESRD because it cannot clear sufficient amounts of oxalate.¹ Theoretically, daily six to eight hour high efficiency haemodialysis sessions would be required, but such a strategy cannot be routinely used. The benefit of haemodialysis (before and) after transplantation is still debated. It should be proposed on the basis of a rapid fall in plasma oxalate; however, weight loss may increase the risk of urinary calcium oxalate supersaturation and therefore it should be limited to patients with severe systemic burden and subsequent long lasting oxalate release from its insoluble pool.⁵

COMBINED LIVER-KIDNEY TRANSPLANTATION

In most cases, isolated kidney transplantation is no longer available for pyridoxine unresponsive patients,¹² and, from the first report in 1985,¹⁶ combined liver-kidney transplantation has been shown to be the only way to replace both the biochemically defective organ (liver) and the pathophysiologically damaged organ (kidney). A total of 98 combined transplantations in 93 patients have been reported so far in Europe, with an average 10 year graft survival of 65%.^{7 17} Various transplant strategies have been advocated using cadaver donors—for example, orthotopic (reduced) liver and simultaneous kidney, orthotopic (reduced) liver alone, orthotopic (reduced) liver alone with delayed kidney.⁷ According to the timing of transplantation in the course of the disease, a living related donor could be considered because of the restricted number of potential biorgan donors. When material for a pre-emptive transplantation is available, such a donor would be proposed for both liver alone and synchronous liver-kidney transplantation. In patients with ESRD and systemic involvement, a metachronous transplantation procedure may be an option because a first step liver transplantation would allow oxalate clearance by vigorous haemodialysis before further kidney transplantation from the same (living related) donor is considered, with a considerably lower risk of early renal damage caused by oxalate released from the body stores.

Ideally, any kind of transplantation should precede advanced systemic oxalate storage. Further assessment of oxalate burden need therefore to be predicted by monitoring sequential glomerular filtration rate, plasma oxalate, and possibly systemic involvement

(bone histology, assessment of bone mineral density by quantitative measures).¹²

REVERSAL OF RENAL AND EXTRARENAL INVOLVEMENT AFTER TRANSPLANTATION

Calcium oxalate in tissues can be remobilised by decreasing the synthesis and increasing the clearance of oxalate according to the accessibility of the oxalate burden to the bloodstream.¹⁸ After combined transplantation, plasma oxalate returns to normal before urinary oxalate; indeed oxaluria can remain for as long as several weeks or months after the transplant.^{2 17} Combined liver-kidney transplantation is therefore able to normalise urinary oxalate with an associated risk of recurrent nephrocalcinosis or renal calculi which may compromise graft function. Forced fluid intake supported by diuretics and the use of crystallisation inhibitor is the most important strategy to protect the kidney. After a successful transplant procedure, damaged organs other than the kidney, such as the skeleton and heart, may benefit greatly from enzyme replacement.^{12 19}

TREATMENT OF PH1 IN INFANTS ACCORDING TO LOCAL NECESSITY

PH1 in early childhood raises specific problems because of (a) the severity of the disease in infants (50% death rate), (b) the diagnostic procedures in this age group, and (c) access to adequate management according to the economic level in each country.²⁰ Infantile PH1 is associated with two opposite issues world wide—that is, a very rare disease in developed countries where combined liver-kidney transplantation is available compared with a common cause of early ESRD in developing countries (because of frequent consanguinity) where therapeutic withdrawal is widely applied.^{7 9 20} Its management is therefore a major example of ethical, epidemiological, technical, and financial dilemmas which may be raised by recessive inherited diseases with early life threatening onset. PH1 can therefore be regarded as one of the rare conditions for which therapeutic withdrawal may be an acceptable option according to local necessity.²⁰

PRENATAL DIAGNOSIS

Prenatal diagnosis from DNA analysis of chorionic villi (10–12 weeks gestation) or amniocytes (15–17 weeks gestation) is possible from either mutational analysis using polymerase chain reaction (PCR) amplification or linkage analysis using the various intragenic and extragenic polymorphisms; the latter is more generally applicable, provided that DNA from the index case and parents is available.^{1 2} Such a procedure allows the identification of normal, affected, and carrier fetuses in most families. In the absence of a valuable index case, the two most common mutations can be checked.⁷

GENE THERAPY

Theoretically, PH1 is a good candidate for gene therapy. It is a progressive chronic disease without involvement of the central nervous

system, most complications are reversible, it is a monogenic disease, the AGT gene is well characterised, and the liver is an easy target for genes. However, there is no good animal model, most hepatocytes are in G₀ phase, and a very high percentage of cells must express transgenically. In addition, several parameters are unknown, such as the consequences of AGT overexpression or ectopic expression.^{2 7}

Non-type 1 PH

In patients with overt hyperoxaluria, the pattern of urinary metabolites is indicative but no longer diagnostic of PH.⁷ In patients with a clinical picture of PH1, 10–30% have normal AGT activity, which may lead to a diagnosis of PH2 or another disorder causing hyperoxaluria.⁷ Measurement of enzyme activity in a single needle liver biopsy can confirm or exclude PH1 and PH2.^{1 2 7 21}

PRIMARY HYPEROXALURIA TYPE 2 (PH2)

Deficiency of the cytosolic glyoxylate reductase/D-glycerate dehydrogenase (GR/HGD) is believed to be the underlying defect.¹ Analysis of liver and lymphocyte samples showed that GR activity was either very low or undetectable, whereas HGD activity was reduced in liver but within the normal range in lymphocytes.²¹ There is evidence for autosomal recessive transmission, and the gene has been located on chromosome 9q11.p11.²²

PH2 has been documented in less than 30 patients, but there are probably some unreported cases.^{23 24} Median age at onset is 15 years.²⁵ In most patients, the classical presentation is urolithiasis, but stone forming activity is lower than in PH1, nephrocalcinosis is less common, and systemic involvement is rare.

The overall long term prognosis is better than for PH1. ESRD occurs in 12% of patients between 23 and 50 years of age.^{23 25} As for PH1, supportive treatment includes high fluid intake, administration of crystallisation inhibitor, and prevention of complications; there is no rationale to use pyridoxine. Kidney transplantation has been performed in some ESRD patients, often leading to recurrence, including hyperoxaluria and L-glycerate excretion.²³ The concept of liver transplantation has therefore been approached, but more data are required on the tissue distribution of the deficient enzyme and the biochemical impact of hepatic GR/HGD deficiency before such a strategy can be recommended.

NON-TYPE 1, NON-TYPE 2 PH

A few reports have shown a possible association of PH (a) without AGT or GR/HGD deficiency or (b) with hyperglycoluria in the absence of AGT deficiency.^{7 26} Such “unconventional” PH may be due to abnormal renal excretion and/or metabolic production. It is therefore likely that there is at least another form of PH yet to be explained.

Conclusion

All children with nephrocalcinosis or urolithiasis should be screened for hyperoxaluria by a laboratory participating in an appropriate

quality control system. Children with hyperoxaluria or recurrent calcium oxalate urolithiasis should be referred for diagnosis and management to specialist clinical centres with interest and experience in the conditions and access to the appropriate biochemical and molecular biological facilities. Major advances in enzymology, genetics, and management have been achieved during recent years in PH. Further research will assess the genotype-phenotype relation and underlying metabolic defects of atypical PH. The continuing analysis of transplant strategies from multicentre databases will improve individual enzyme replacement and subsequent patient survival and quality of life.

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EUROPE CALLING

Unnoted by the great majority of the general paediatric community, the “5th International Conference on Pediatric ORL” scheduled to be held in Graz, Austria, 9–12 July 2000, has been cancelled. In his letter to those colleagues organising scheduled symposia, the congress chairman, Prof Stammberger, head of the department of head and neck surgery at the University of Graz, bitterly regretted this unforeseen development.

What had happened? Obviously, the current political situation in Austria had resulted in the several international pharmaceutical companies withdrawing their participation in the meeting, shortly after a new government had been elected to include the ultranationalist Jörg Haider’s FPÖ (Liberal Party of Austria). One may argue whether it is politically correct to participate in an international medical convention in a country whose government contains politicians from a party whose leader (Haider himself is not a member of the government) has repeatedly expressed antisemitic and other discriminating statements. However, international medical meetings used to be and are still being held in non-democratic countries (which Austria is

not) with financial support from the pharmaceutical industry and generally without boycott from potential attendees.

It is sad that scientific exchange—that is, the realisation of a long planned European meeting, has to suffer from the admittedly unwelcome political development in Austria. What is of concern is the fact that it was not the scientist’s decision to refrain from participation but that of the sponsors from the pharmaceutical industry, who feared for their international reputation. Today, most national and virtually all large international medical conventions depend on direct (sponsoring of speakers) and indirect (through participation in parallel exhibitions) financial support by industry. Probably, there is little we can do about it and usually this is acceptable as long as the organising committees remain independent. But at least it should be a warning for all future organisers of meetings to be alert when they sign contracts with sponsors.

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