Primary Hyperoxaluria Type 1: Genotypic and Phenotypic Heterogeneity

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Summary: Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disease caused by a deficiency of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT). The disease is notable for its extensive heterogeneity at the clinical, biochemical, enzymic and molecular genetic levels. A study of 116 PH1 patients over the past 8 years has revealed four main enzymic phenotypes: (1) absence of both AGT catalytic activity and immunoreactive AGT protein (~40% of patients); (2) absence of AGT catalytic activity but presence of immunoreactive protein (~16% of patients); (3) presence of both AGT catalytic activity and immunoreactive protein (~41% of patients), in most of which cases the AGT is mistargeted to the mitochondria instead of the peroxisomes; and (4) a variation of the mistargeting phenotype in which AGT is equally distributed between peroxisomes and mitochondria, but in which that in the peroxisomes is aggregated into matrical core-like structures (~3% of patients). Various point mutations, all occurring at conserved positions in the coding regions of the AGT gene, have been identified in these patients. The five mutations discussed in the present study, which have been found in individuals manifesting all of the four major enzymic phenotypes, account for the expressed alleles in about half of all Caucasian PH1 patients. The most common mutation found so far leads to a Gly170 → Arg amino acid substitution. This mutation, in combination with a normally occurring Pro11 → Leu polymorphism, appears to be responsible for the unprecedented peroxisome-to-mitochondrion mistargeting phenotype.

PH1 AND AGT DEFICIENCY

Primary hyperoxaluria type 1 (PH1, McKusick 259900) is a rare autosomal recessive inborn error of glyoxylate metabolism, characterized biochemically by increased synthesis and excretion of oxalate and glycolate, and clinically by the deposition of insoluble calcium oxalate, initially in the kidneys as urolithiasis and/or nephrocalcinosis, but, following renal failure, also throughout the body as systemic oxalosis (Williams and Smith 1983). The increased synthesis of oxalate and glycolate is caused by a deficiency of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT, EC 2.6.1.44), the normal role of which is to catalyse the
transamination (detoxification) of glyoxylate to glycine, using alanine as the amino donor (Danpure and Jennings 1986). AGT deficiency in PH1 allows the glyoxylate to be oxidized to oxalate within the peroxisome, catalysed by glycolate oxidase (GO, EC 1.1.3.15), or to diffuse through the peroxisomal membrane into the cytosol, where it is oxidized to oxalate, catalysed by lactate dehydrogenase (LDH, EC 1.1.1.27) and reduced to glycolate, catalysed by glyoxylate reductase (GR, EC 1.1.1.26/79) and possibly also LDH (Danpure and Jennings 1986; Danpure 1989).

CLINICAL HETEROGENEITY

The clinical manifestations of PH1 are quantitatively and qualitatively heterogeneous with respect to the timing, rate of progression and relative contribution made by each of the pathological sequelae (Danpure 1991). In most patients, the first symptoms occur in early childhood due to the presence of urolithiasis. However, there is an enormous spread in the ages at which the disease first becomes apparent; it can be as early as the first few months of life or as late as the seventh decade. Typically, PH1 is a progressive disease; renal deposition of calcium oxalate continues inexorably, accompanied by a gradual deterioration of renal function, until end-stage renal failure in late childhood or early adulthood. Before the introduction of modern treatment methodologies (e.g. hepatorenal transplantation; Watts et al 1987, 1991), it has been estimated that 80% of PH1 patients died from renal failure before the age of 20 years (Williams and Smith 1983).

A minority (probably less than 10%) of patients have a much more severe form of the disease, sometimes called acute neonatal PH1. These patients typically present in the first few months of life with renal failure due to nephrocalcinosis without urolithiasis (Leumann 1985). Progression of the disease is very rapid and such patients frequently die before the end of the first year of life.

Although concomitant hyperoxaluria and hyperglycolic aciduria are the biochemical hallmarks of PH1, the relative proportions of these glyoxylate metabolites found in the body fluids of patients vary over a wide range. Some patients with proven AGT deficiency have isolated hyperoxaluria with no evidence of elevated glycolate synthesis (Danpure 1991), whereas others have marked hyperglycolic aciduria with only mild hyperoxaluria (Watts et al 1983).

Pyridoxal phosphate is an essential cofactor for AGT. Some PH1 patients (10–30%) are pyridoxine-responsive insofar as their oxalate excretion can be significantly lowered and their clinical symptoms can be markedly improved by the chronic administration of pharmacological doses of pyridoxine (Ludwig 1963; Gibbs and Watts 1970).

ENZYMATIC HETEROGENEITY

AGT expression

The wide clinical heterogeneity of PH1 is matched by its equally wide enzymic heterogeneity (Danpure 1991; Danpure and Jennings 1988). In the present study, 49 of the 116 patients were found to have undetectable levels of immunoreactive AGT protein (CRM−) (Figures 1 and 2). Of the remaining 67, who did possess