Hyperoxaluria Type I: Therapeutic Effects of Pyridoxine Hydrochloride and Inheritance Patterns of the Disease in a Family

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Summary: The cases of two patients with primary hyperoxaluria type I, aged five years and two years, born to consanguineous parents are described. These patients have been treated with oral pyridoxine hydrochloride at a dose of 200 mg/24 hr without evidence that this regimen has decreased urinary oxalate excretion. Studies of oxalate excretion in the family members yielded results consistent with either autosomal dominant inheritance, with variable expressivity, or with autosomal recessive character.

Key words: urolithiasis in infancy—primary hyperoxaluria type I—pyridoxine—mode of inheritance—glycolate

Introduction

Primary hyperoxaluria has been classified into two specific entities; type I and type II (Williams and Smith, 1983). Type I disease is caused by a defect in either soluble 2-oxoglutarate: glyoxylate carboxylase (Koch et al. 1967) or peroxisomal alanine: glyoxylate aminotransferase (Danpure and Jennings, 1986; Danpure et al. 1987). While in type II disease, a deficiency of D-glyceric dehydrogenase has been demonstrated (Williams and Smith, 1983). These diseases often present with urolithiasis and hematuria in infancy and progress to chronic renal failure in later stages. In type I disease, synthesis of not only oxalate but glycolate is enhanced (Fig. 1), and the excessive oxalate syn-

thesis may eventually result in deposition of calcium oxalate in the kidney and extrarenal tissues, presenting as a condition termed oxalosis.

Pyridoxine in large doses has been administered to several patients with this disease, resulting in significant decreases in oxalate excretion in some of the patients (Gibbs and Watts, 1970; Gill and Rose, 1986; Morgan et al. 1987). This pyridoxine-induced decrease in oxalate excretion is presumably effected through the depletion of the glyoxylate pool by conversion to glycine. Glyoxylate undergoes transamination to glycine with alanine (Danpure and Jennings, 1986) in a reaction which requires pyridoxalphosphate as a cofactor (Fig. 1). It is not known, however, whether or not pyridoxine can pre-

Fig. 1. Metabolic pathway of glyoxylate.

Enzymes involved: (1) 2-oxo-glutarate: glyoxylate carboligase, (2) alanine: glyoxylate aminotransferase, (3) D-glycercic dehydrogenase.

vent or retard the progression of the renal disease.

Type I disease is generally thought to be inherited in an autosomal recessive manner (Hockaday et al. 1964), although in some pedigrees, dominant inheritance has been suggested (De Toni and Durand, 1959; Shepard et al. 1960).

We describe in this report the effects of pyridoxine on oxalate excretion in two siblings with type I hyperoxaluria, and present results of a genetic study in this family.

Methods

Oxalalate in urine was determined by gas chromatography with malonic acid as an internal standard (Yachiku and Kamidate, 1985). The other organic acids in urine, including glycolate and glycerate, were extracted and derivatized as previously described (Tanaka et al. 1980) and analyzed by gas chromatography-mass spectrometry (GC/MS).

Case Reports

Patient 1.

The proband D.H. (87-2350), a five year and four month-old boy, was referred to Kurume University Medical Center because of nephrolithiasis. He was born to consanguineous parents after an uneventful pregnancy and delivery at 38 weeks of gestation. The birth weight was 3.030 g. He has achieved developmental milestones normally. He has had several episodes of fever of unknown cause in early infancy. Because he suddenly became unable to void at the age of five years and four months, he was brought to a local clinic, where multiple radiopaque urinary calculi were found. He was referred to us for further evaluation of the urolithiasis four months later.

Other than shortness of stature (height at the 3 percentile level), there were no positive findings upon physical examination at admission.

Urinalysis was negative for both protein and glucose, and the sediment con-

Fig. 2. (A) Total ion current chromatogram, (B) top, mass spectrum of sample chromatogram peak #107, and (B) bottom, mass spectrum of authentic ditrimethylsilylglyoxylate.

tained 0 to 20 erythrocytes, and numerous leukocytes per high-power field. Concentrations in serum of creatinine and urea nitrogen were 0.8 mg/dl and 15.0 mg/dl, respectively. Renal function studies revealed the following: creatinine clearance 49 ml/min/1.73 m², excretion of phenol-sulfonphthalein 2.1% at 15 min and 20.5% at 120 min, fractional excretion of sodium 0.62 to 2.18%, and tubular reabsorption of phosphate 65 to 73%. There were minimal increases in urine cystine, arginine, ornithine, methionine and proline. Concentration of β_2 -microglobulin was 3220 μ g/l in urine. Liver function tests, blood counts, and blood gas values were within respective normal ranges. The plain abdominal x-ray disclosed multiple clusters of radiopaque lesions consistent with urolithiasis. Bone age was at the level of two years of chronological age. Analysis of a passed stone revealed that it consisted exclusively of calcium oxalate. Excretion of oxalate in urine ranged from 78 to 89 mg/24 hr, or from 204 to 232 mg/24 hr/1.73 m², whereas the normal range for adults is 10 to 45 mg/24 hr (Yachiku and Kamidate, 1985). Massive excretion in urine of glycolate was found, but L-glycerate was undetectable (Figs. 2A and 2B). This profile of urinary

organic acids led us to the diagnosis of primary hyperoxaluria type I.

Patient 2.

A younger brother of the proband, T.H. (88-80), who has been growing normally without any clinical signs, was found to have an elevated level of urinary oxalate and urolithiasis at the age of two years and two months, while the family was being surveyed.

Physical examination revealed no abnormality. Urinalysis showed 7 to 8 erythrocytes and numerous leukocytes per high-power field. Serum levels of creatinine and urea nitrogen were 0.4 mg/dl and 8.9 mg/dl, respectively. Serum electrolytes and blood gas values were within respective normal ranges. X-ray of the abdomen revealed multiple calcified lesions. Amounts of oxalate excreted in urine ranged from 39 to 101 mg/day or from 129 to 336 mg/24 hr/1.73 m².

Family Study

The proband was born of consanguineous parents (Fig. 3). Studies of family members revealed that father, paternal grandfather, and sister of the proband were hyperexcretors of oxalate. Although

Fig. 3. Pedigree chart.

Note relation of maternal great-grandmother and paternal grandmother (paternal grand mother (II-2) and maternal great-grandmother are cousins once removed).

Fig. 4. Effects of pyridoxine hydrochloride on oxalate excretion in the proband (A) and the younger brother (B). Lines indicate oxalate levels, and the stippled columns represent dose of pyridoxine hydrochloride.

normal ranges of oxalate excretion for children have not been clearly established, the excretion of oxalate corrected for body surface area seems to be comparable to that in adults (Gibbs and Watts, 1969). The sister of the proband was therefore interpreted to be a hyperexcretor.

Responsiveness to Pyridoxine hydrochloride

We evaluated possible effectiveness of pyridoxine hydrochloride in the proband and the younger brother. The proband received 100 mg/day of pyridoxine hydrochloride for the initial three months of treatment and has been receiving 200 mg/day subsequently without significant change in oxalate excretion (Fig. 4A). Patient 2 has been given 200 mg/day of the same preparation. Although oxalate excretion decreased transiently immediately after the introduction of pyridoxine therapy, it rose again within two months to the pre-treatment level (Fig. 4B).

Discussion

Hyperoxaluria type I often presents with hematuria or urolithiasis in infancy. This disease often progresses to renal failure

in adulthood in the majority of patients, but renal failure may become overt at an earlier stage. The major therapeutic goal in combatting this disease is therefore the prevention or amelioration of renal failure.

Pyridoxine in large doses has been tried for this purpose (Gibbs and Watts, 1970; Gill and Rose, 1986; Morgan et al. 1987). Glyoxylate, the immediate precursor to oxalate, is converted to glycine mainly by alanine: glyoxylate aminotransferase, a pyridoxine dependent enzyme (Fig. 1), and deficiency of this enzyme has been demonstrated in some of the patients with hyperoxaluria type I (Dunpure and Jennings, 1986; Dunpure et al. 1987). Enhancement of the activity of this enzyme by pyridoxine would increase glyoxylate conversion to glycine, resulting in a diversion in the glyoxylate pool which is otherwise converted to oxalate.

Reduction of oxalate excretion by pyridoxine has been demonstrated in a number of patients, but effect of the vitamin on overall clinical status has not been documented in such patients. Failure to improve clinical status by pyridoxine therapy in the majority of these patients may be partly due to the fact that treatment was started after renal damage had developed.

In the proband of the present family, pyridoxine at a dose of 200 mg/day did not appear to decrease oxalate excretion. In the younger brother there was a transient decline in oxalate excretion immediately following the start of pyridoxine administration, followed by an increase. Follow up for a longer period and with larger doses of the vitamin appears to be necessary to evaluate efficacy of this regimen in our patients.

Primary oxaluria type I is presumed to be inherited in an autosomal recessive manner in the majority of reported pedigrees (Hockaday et al. 1964; Williams and Smith, 1983). There are, however, some exceptional pedigrees in which the trait is transmitted in a mode consistent with autosomal dominance (De Toni and Durand, 1959; Shepard et al. 1960). In the family of our patients (Fig. 3), two siblings of the proband are hyperexcretors of oxalate, and in addition, the younger brother exhibited radiopaque lesions consistent with nephrolithiasis.

In previously studied families in which autosomal recessive mode of inheritance of this disease is suspected, urinary oxalate excretion has been almost invariably normal in parents of patients (Hockaday et al. 1964). In contrast to this, father and paternal grandfather of the proband in this case excreted oxalate in abnormally increased amounts but in smaller amounts than those generally observed in patients (Hockaday et al. 1964).

The mother's oxalate excretion was normal. These observations imply that in this particular family the disease is transmitted as an autosomal dominant character with a variable expressivity. However, in view of the fact that paternal grandmother (Fig. 3, II-2) and maternal great grandmother (Fig. 3, I-2) of the proband were related, it is also possible that this disease is inherited autosomal recessively, the parents of the proband being heterozygous, and the offspring, at least the proband and

the younger brother, homozygous for this disease trait. In this situation, the moderate hyperoxaluria in father and paternal grandfather may be explicable as the product of heterozygous effect.

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