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Primary hyperoxaluria type I

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Abstract. Primary hyperoxaluria type I is a metabolic disorder caused by the deficiency of the peroxisomal alanine:glyoxylate aminotransferase. The disease is inherited as an autosomal recessive trait. The clinical course is outlined based on data from 330 published cases. Diagnostic cornerstones are clinical parameters, urinary excretion of oxalate and glycollate, and the determination of enzyme activity in liver tissue. Principles of conservative treatment, e.g. volume load and pyridoxine substitution, are described as well as experience with different modes of dialysis and transplantation. Kidney transplantation is associated with a high rate of recurrence of the original disease despite excellent management resulting in many instances in early graft loss. Liver transplantation offers the possibility to correct the metabolic defect and to prevent the progression of crystal deposition in the body.

Key words: Alanine:glyoxylate aminotransferase – Hyperoxaluria – Oxalate – Transplantation

Introduction

Hyperoxaluria is a rare condition which may be primary or secondary. The disorders gain medical attention because of the extremely low solubility of calcium oxalate leading to crystal formation, mainly in the urinary tract, urolithiasis and nephrocalcinosis.

The primary hyperoxalurias are classified as at least two different subtypes [41]. Primary hyperoxaluria type I (McKusick 25990) is a rare genetic disorder caused by the deficiency of the alanine:glyoxylate aminotransferase (AGAT). Primary hyperoxaluria type II (McKusick 26000) is caused by a defective D-glycerate dehydrogenase [63]. Only eight cases have been published since the initial description [14].

Primary hyperoxaluria type I is a peroxisomal disorder [45, 56] and is classified into three groups each defined by the degree of loss of peroxisomal function [56]. Only two of the peroxisomal diseases do not affect the central nervous system: acatalasaemia and primary hyperoxaluria type I. Whereas in Zellweger syndrome peroxisomes are absent, in primary hyperoxaluria they are only reduced in number and size [32].

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Abbreviation: AGAT = alanine:glyoxylate aminotransferase

History

Since Lepoutre published the first case of oxalosis [35], numerous reports have appeared on the course and origin of the disease. About 30 years ago Archer and coworkers [4] presumed a metabolic defect as the cause of the disease. In 1967 Koch and Stokstad [33] described a deficiency of cytosolic 2-oxo-glutarate carboligase in a patient with hyperoxaluria. The fact that thiamine was the cofactor for this enzyme and a girl was described with classical hyperoxaluria without deficiency of 2-oxoglutarate carboligase [7], raised questions which remained unsolved for the next 20 years. Eventually in 1986, Danpure and Jennings located the correct enzymatic defect of the disorder [17, 19].

Enzymatic defect

The deficient AGAT is located in liver peroxisomes (Fig. 1). Activity of the enzyme is almost absent in

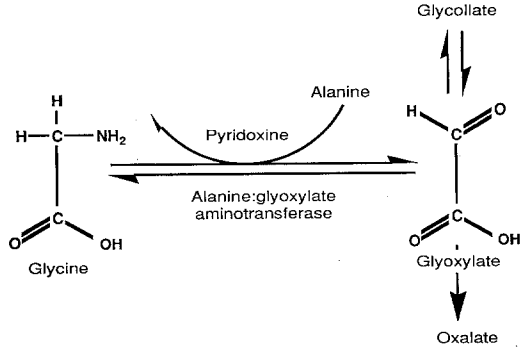

Fig. 1. The metabolic defect in primary hyperoxaluria type I. The alanine:glyoxylate aminotransferase (EC 2.6.1.44) is located in the peroxisomes of the liver

affected individuals [18]. Residual activity correlates with a milder course [57]. Genetic heterogeneity was found by Wise et al. [65] who demonstrated functionally inactive protein immunologically the same as the deficient AGAT. Meanwhile a third subtype has been studied by the same group demonstrating that subcellular mislocation of the enzyme into mitochondria results in hyperoxaluria in at least 3 out 27 affected individuals [21].

Mode of inheritance

The defect is inherited as an autosomal recessive trait [38]. Only few reports suggest other modes of inheritance [52]. In a study of 330 patients [34] family data were available in 231. There were affected family members in 90, consanguinity in 18, and non-hyperoxaluric nephrolithiasis without renal failure in 55 parents or siblings.

Incidence of the disease

The incidence of the disease is unknown and hard to estimate. Reliable data are available for the incidence of end-stage renal failure for the disorder. In the registry of the European Dialysis and Transplantation Association about 1% of children developing end-stage renal disease every year account for primary hyperoxaluria [50]. Our data show 2%–2.7% of children with hyperoxaluria among those developing end-stage renal disease [11, 46]. These data are comparable to those of the Arbeitsgemeinschaft für pädiatrische Nephrologie for 1979–1982 [47, 48]. Assuming five to six children developing end-stage renal disease per million children and year, the incidence of primary hyperoxaluria with renal failure can be assumed to be of 1 in 5–15.000.000 children between 0 and 15 years. This figure probably underestimates the true incidence of the disease, but no data for a more reliable estimate are available.

Symptoms and course

Initial symptoms usually occur in early childhood. First signs of the disease are present in 50% of children before age 5 [28]. Up to 25 years, 90% of patients are symptomatic. Figure 2 depicts the age of first symptoms, although the diagnosis is usually made much later. The first symptoms ($n = 260$) consist of urolithiasis in 64.2% of cases, 14.2% being already uraemic when the diagnosis is made. Especially infants demonstrate different symptoms. Failure to thrive is the leading symptom in this age group while urolithiasis is rare, occurring only in 3 out of 43 [36]. In only 11 out 90 patients with family members carrying the disease was diagnosis made prior to initial symptoms.

During disease progression recurrent urolithiasis is usually noted. The number of stones passed ranges from 1 to more than 100. During the course of the disease almost all patients develop end-stage renal failure. By

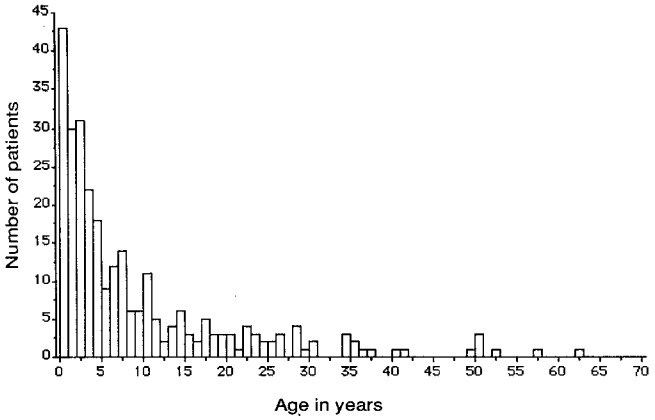

Fig. 2. Age of patients with primary hyperoxaluria type I when first symptoms occurred ($n = 276$) [32]

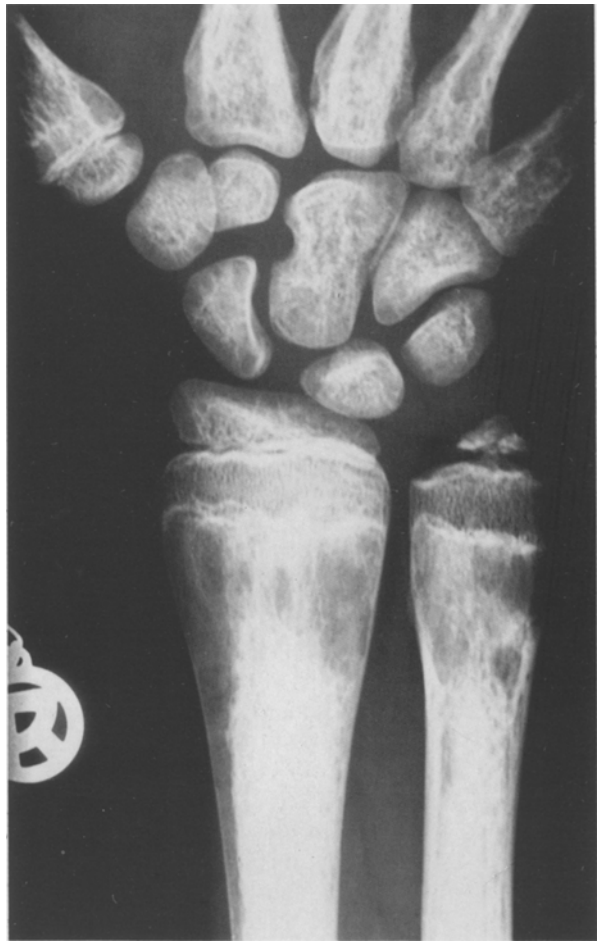

Fig. 3. Right hand of a 12-year-old girl with hyperoxaluria type I, 3 years after renal failure developed and 1 year after renal transplantation. Most bones of the wrist demonstrate bone-in-bone phenomena while the metaphyseal bands are clearly seen in both radius and ulna

15 years of age, 50% of children have reached terminal renal insufficiency. By the end of the 3rd decade 80% of patients require renal replacement therapy [34]. Most patients develop renal failure over a rather short period of time. The usual course is less than 2 years from an

almost normal function to endstage renal disease [51]. Repeatedly, the attempt to remove a single stone without knowledge of the metabolic disorder resulted in a rapid progression to terminal renal failure within a few weeks. Proper perioperative management prevents this course.

Physical development including growth is not impaired until renal function deteriorates. During the phase of renal insufficiency oxalate accumulates in the body of these patients. Oxalate starts to accumulate at slightly impaired renal function levels [44] and is deposited in various tissues. Severe bone problems occur in most patients as soon as the renal function is markedly impaired [1, 6, 9]. The bones become dense, bone-in-bone phenomena become visible and almost pathognomonic radiolucent metaphyseal bands develop within 1 year of severely impaired renal function (Fig. 3) [22]. Additionally, calcium oxalate crystals are found in the media of the arteries and calcified vessels are sometimes seen on native X-ray films [8]. Discolouration and even gangrene of the affected extremities may result [3, 55]. Life-threatening complications are caused by oxalate deposition in the conduction system of the heart [5, 16]. In 50% of all patients dying on dialysis the cause of death was sudden untreatable arrhythmias, mainly third degree AV-block [31]. Especially in the infantile type of primary hyperoxaluria, calcium oxalate crystals appear as druses in the chorioidea and are detectable on fundoscopy [26, 54]. This is rather rare in older patients. Oxalate deposition has been described in almost all other organs except the liver [23, 30, 43]. It is not clear whether oxalate is deposited in the brain.

Diagnosis

The diagnosis of primary hyperoxaluria is suggested by a combination of renal failure in a child or young adult, a history of urolithiasis, a family history for urolithiasis, consanguinity, and nephrocalcinosis. In infants, failure to thrive is a prominent feature of the disease and ultrasound to detect the nephrocalcinosis may be of special value [10, 64]. The classical way to establish the diagnosis of primary hyperoxaluria is the measurement of the excretion of oxalate and glycollate in the urine by various methods [29]. An urinary excretion of 50 mg oxalate/day per 1.73 m^2 body surface is considered the upper limit of normal. While slightly elevated excretions are inconclusive, values twice as high are highly suspicious for primary hyperoxaluria, especially in absence of ingestion of oxalate, its precursors or malabsorption. The concomitant measurement of glycollate proves the diagnosis. Excretion of more than 70 mg/day per 1.73 m^2 of glycollate is considered pathological. Errors are made by ignoring the age and body surface area of the patient. Additionally, renal failure diminishes the excretion of oxalate reducing excreted amounts even in hyperoxaluric subjects to normal values [44]. The demonstration of elevated ratios of oxalate/creatinine (normal for infants: 26–268 mmol oxalate/mol creatinine) and glycollate/creatinine (normal for infants: 22–72 mmol glycollate/mol creatinine) are helpful in these patients and in infants where usually no correct urine collection is possible [37]. In single urine samples recent ingestion of oxalate-rich food may lead to short but sharp rises in the concentration of oxalate.

In anuric renal failure the diagnosis can be proven by liver biopsy and measurement of the enzyme activity. Enzyme activity, absence of immunoreactive enzymatic material and mislocation of the enzyme can be demonstrated [20].

Antenatal diagnosis is difficult. Oxalate and glycollate levels in amniotic fluid are normal regardless of the metabolic status of the fetus [37]. Measureable activities of the enzyme are only expressed in liver peroxisomes. Therefore fetal liver biopsy with consecutive measurement of the activity of the AGAT is the only way to establish the diagnosis. The procedure has been proven successful although it has been pointed out that analysis of subcellular location of the enzyme is not possible because of the extremely small amount of material gained by the procedure [21]. Therefore mislocation of the enzyme into the mitochondria may result in false results limiting the value of the procedure.

Treatment

The main objective of treatment is good hydration at any time. Excessive volume is necessary to excrete the enormous amounts of endogenously produced oxalate. Dietary restriction of oxalate-rich foods is helpful, but does not reduce oxalate excretion decisively.

In cases with residual enzymatic activity, pyridoxine can substantially reduce the production and therefore excretion of oxalate [2, 67, 68]. The usual daily dose is 1000 mg/m^2 body surface area. Unfortunately most patients have pyridoxine-resistant forms of the disease. Attempts to reduce the production of oxalate with succinimide, allopurinol, calcium carbimide, and isocarbacide have been unsuccessful [27, 58]. Magnesium, phosphate, and methylene blue reduce the formation of calcium oxalate crystals in vitro. In one study magnesium oxide showed good clinical effects [53]. The positive effect of oral phosphate has to be questioned; depending on the dosage oxalate resorption seems to be increased [49]. Long-term use of calciuretic diuretics like furosemide is harmful, and therefore thiazides are the diuretics of choice [51].

Dialysis

If renal replacement therapy has to be instituted, haemodialysis is superior to any kind of peritoneal dialysis. Only 70–90 mg of oxalate is removed by a four-exchange continuous peritoneal dialysis, equalling an oxalate clearance of about 7 ml/min [59, 66]. During a 5 h haemodialysis 300–550 mg of oxalate can be removed [39]. The amount removed depends on the serum level of oxalate. 6 h haemodialysis can cope with the daily oxalate production of a hyperoxaluric subject [59]. Be-

cause daily haemodialysis is not feasible in a long-term clinical setting, no dialysis procedure is able to prevent the development of generalized oxalosis [42]. Therefore early transplantation is mandatory. The conceptual work by Morgan et al. [44] suggests that definite replacement should be planned for when the creatinine clearance drops below 40 ml/min and carried out when the clearance has fallen under 20 ml/min.

Transplantation

During the past 2 decades more than 80 patients have undergone renal transplantation. The overall success rate was much lower than in other diseases, mainly because of recurrent primary disease. The transplantated kidney is usually exposed to large amounts of oxalate. The time on dialysis prior to transplantation, initial dysfunction, and rejection episodes are factors endangering graft survival. While the registry of the European Dialysis and Transplantation Association shows only a 23% graft survival after 3 years [12], a survey of 70 published cases showed twice this survival rate [34]. Special peri-operative care as initially demonstrated by Scheinman et al. [51] and proper timing of transplantation [62] improve the results, but in general, kidney transplantation seems to offer only temporary relief. It does not prevent the progression of bone problems and vascular disease, though reports are conflicting [22, 24, 51, 55].

Definite correction of the metabolic lesion can be offered by liver transplantation [61]. Biochemical studies demonstrate a metabolic normalization shortly after transplantation [60]. Accumulated oxalate is mobilized and excreted over months whereas glycollate, which does not accumulate, is excreted in normal amounts immediately after liver transplantation. Only in case of no prior accumulation do both excretions return to normal immediately after liver transplantation [15]. Judging from the survival rate of 85% 3 years after liver transplantation for other metabolic defects [13] the risk of liver transplantation should be acceptable. In most cases the procedure was carried out as combined kidney and liver grafting. Though this leads to additional management problems than in cases of single organ dysfunction, combined grafting is immunologically superior and severe renal dysfunction as a major risk factor in liver transplantation can be avoided [25]. Different strategies have been tried to optimize the outcome. In case of residual renal function of the patients kidneys, liver transplantation should be carried out before terminal renal failure occurs [15]. A recent report shows the reversibility of oxalosis-related complications after sequential grafting with complete resolution of oxalate crystals in the kidney [40]. Whether such excellent course can be expected in the majority of the patients requires further studies.

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