



Hyperoxaluria, Primary, Type I

Alternative Names

HP1
Oxalosis I
Glycolic Aciduria
Alanine-Glyoxylate Aminotransferase Deficiency
Peroxisomal Alanine:Glyoxylate Aminotransferase Deficiency
Hepatic AGT Deficiency
Serine:Pyruvate Aminotransferase Deficiency

Record Category

Disease phenotype

WHO-ICD

Endocrine, nutritional and metabolic diseases >
Metabolic disorders

Incidence per 100,000 Live Births

0-1

OMIM Number

259900

Mode of Inheritance

Autosomal recessive; two separate loci

Gene Map Locus

2q36-q37

Description

Primary hyperoxaluria type I (HP1) is a rare metabolic disorder that causes very high levels of endogenous oxalate production (>200 mg/d). HP1 occurs due to a defect of the peroxysomal hepatic enzyme L-alanine:glyoxylate aminotransferase (AGT) that catalyzes the conversion of glyoxylate to glycine. AGT deficiency results in high glyoxylate level, which is converted to oxalate. Excess oxalate forms insoluble calcium salts that accumulate in the kidney and other organs. Therefore, patients with HP1 are at high risk to have recurrent nephrolithiasis (deposition of calcium oxalate in the renal pelvis/urinary tract), nephrocalcinosis (deposition of calcium oxalate in the renal parenchyma), or end-stage renal disease with a history of renal stones or calcinosis.

Urolithiasis increases by infections, hematuria, renal colics or acute renal failure due to complete obstruction. High level of circulating oxalate in end-stage renal failure leads to the deposition of oxalate in tissues causing cardiac conduction defects, hypertension, distal gangrene, and reduced joint mobility and pain. Onset of symptoms ranges from one to 25 years, but about 15% have the initial symptoms at less than one year of age and they present severe disease. The infantile form of the disease is characterized by chronic renal failure resulting from massive oxalate deposition. HP1 occurs in 1 per 120,000 live births worldwide and white persons are more likely to have the disease. Also, men have three times more kidney stones than women.

Treatment includes high fluid intake to maintain high urine output, pyridoxine supplement (AGT coenzyme) and alkalization of urine. Curative treatment involves combined kidney and liver transplantation. However, if early liver transplantation is done, the native kidneys can be preserved and avoiding kidney transplantation.

Molecular Genetics

Primary hyperoxaluria type I (HP1) is transmitted as an autosomal recessive trait. The only gene considered to be associated with HP1 is the gene that encodes for alanine-glyoxylate aminotransferase (AGT or AGXT gene). In about one-third of people with HP1, AGT enzyme is misplaced within the cell due to the combination of certain mutations with a natural variation (polymorphism) in the AGT gene. This combination alters the structure of the AGT enzyme and, therefore, reduces its activity within hepatic cells. Over 40 mutations in AGT gene have been reported; however, most of them are private and specific to a certain family. The most common disease-causing mutation is the G170R mutation which is associated with mistargeting of AGT to the mitochondria instead of locating in the peroxisomes of hepatic cells.

Epidemiology in the Arab World



Bahrain

Lyth (1988) compared the urinalysis results of 50 Bahraini male patients who passed, or had calcium, oxalate or phosphate stones removed, with 50 control male and 50 control female subjects. Findings revealed that the stone formers excreted oxalate significantly more than the normal controls. This was in contrast to reports from Western literature that demonstrated hypercalcuria and only mild hyperoxaluria. The mean urine volume was also significantly higher for the stone formers. Lyth (1988) also compared the tea drinking habits of Bahrainis and other Asians, but could decipher no significant differences. He suggested that the dietary intake of oxalate by Bahrainis is significant, only of the animal protein intake is taken into account.

Kuwait

Al-Eisa et al. (2004) conducted a retrospective study of all children less than 16 years of age with end-stage renal disease treated in the pediatric nephrology unit in Kuwait over a period of 8 years (January 1995 to December 2002). Of the 48 children boys comprises 52% and the overall mean age at institution of dialysis was 94.4 months. Causes of renal disease included congenital structural anomalies in 52%. Hereditary nephropathy was diagnosed in 35.4%, including primary hyperoxaluria in 10.4%, nephronophthisis in 2%, autosomal-recessive polycystic renal disease in 8%, and glomerulopathies in 14.5%. The mortality rate in the dialyzed group was 16%. Twenty-four patients received kidney transplants from, cadaveric donors in 19 cases. Al-Eisa et al. (2004) indicated that genetic factors contributed to the high incidence of end-stage renal disease, which is most likely due to the common practice of consanguineous marriages in the country.

Oman

Hauggaard and Ekelund (2000) reported a 13-year-old Omani boy in the UAE who was diagnosed to have primary hyperoxaluria type I (HP1). He was born to second cousins parents and he had a sibling with hyperoxaluria who died at three years from end-stage renal failure. Echocardiogram, ultrasound, CT, and X-ray were performed. The patient had cardiomyopathy which was induced by chronic renal failure, small kidneys with nephrocalcinosis, oxalate crystals in the bone marrow, and generalized osteoporosis. He was treated with hemodialysis, diuretics, restricted fluid regime, and CaCO₃. Three years later, the patient developed convulsions during hemodialysis, and the EEG showed multi-focal epilepsy. After six months, he had a fracture of the right femoral neck. When he was 19 years old, he had skeletal pain, and hyperparathyroidism. After three weeks of vitamin

D treatment, the serum parathyroid hormone became normal. Hypogonadism and growth retardation were below the fifth percentile for age and sex. Retardation of bone age, development of sclerotic vertebra, and calcified small kidneys were also observed. There were translucent metaphyseal bands of rarefaction with sclerotic margin at the end of long bones as a sign of disorder of bone growth. Metaphyseal sclerosis was also found in the proximal end of the phalanges and the distal end of the metacarpal bones.

Saudi Arabia

Sanjad et al. (1999) reported their findings in 16 children diagnosed with PHI over a 10-year period ending in June 1997 to emphasize the role of early diagnosis, aggressive medical management, pyridoxine therapy and organ transplantation in the prevention and treatment of affected patients. Clinically, nephrolithiasis and nephrocalcinosis were present in the majority of patients. Four patients had advanced chronic renal failure at the time of diagnosis, with variable degrees of systemic oxalosis. Urinary tract infection, abdominal pain and hematuria were relatively common. None of the patients included in the study presented with the infantile form of PHI. The diagnosis was made by quantitative urinary oxalate excretion in 24-hour urine collections in seven patients, where the mean excretion rate was 1.7 ± 0.2 mmol/1.73m²/24hr (normal <0.5 mmol/0.173 m²/day). In another seven patients, the diagnosis was made by "spot" urine oxalate/creatinine mmol ratios, with a mean of 0.67 ± 0.17 (normal <0.15). Also, urine glycolate was detected qualitatively by gas chromatography and glycolic aciduria was present in all four patients tested. In two patients with advanced chronic renal failure and equivocal urinary oxalate excretion, the diagnosis was established by bone marrow aspiration, which showed extensive oxalate crystal deposition in the bone marrow, characteristic of PHI. Once the diagnosis of PHI was established, patients were instructed to drink a minimum of 2 liters of water/m²/day. The median age of presentation of PHI was five years (5 months-13 years). The interval from the onset of symptoms to diagnosis ranged from 0 (screening of asymptomatic siblings) to 4 years, with a median of 18 months. Sanjad et al. (1999) referred the reasons for delaying in the diagnosis of PHI to the rarity of the disease and hence the lack of suspicion. Also, the measurement of urinary oxalate and glycolate is limited to university hospitals and reference laboratories, further adding to diagnostic delays in areas where these are not available. Thus, Sanjad et al. (1999) emphasized the importance of the early clinical diagnosis of PHI by measuring urinary oxalate excretion in any child with a history of urinary tract stones, particularly if associated



with nephrocalcinosis, a normal urinary calcium excretion, a positive family history and parental consanguinity. This series of 16 patients included nine patients from three families, all products of consanguineous parents. In each of these families, the identification of the proband led to the detection of asymptomatic siblings. Thus, a total of seven patients were diagnosed by sibling screening of known patients with PHI. Four had nephrocalcinosis with asymptomatic renal calculi, and three had only elevated urinary oxalate excretion. Eight patients underwent organ transplantation during this study. A 15-year-old patient underwent a successful kidney transplant from his mother. By contrast, the outcome of kidney transplantation in other two younger patients, ages 7 and 7½, was associated with early loss of graft and subsequent death from complications of systemic oxalosis. The three patients who underwent combined liver/kidney transplantation have had excellent results, with normal or mildly renal function at five years post-transplantation. Two patients underwent liver transplantation. One patient survives and has a normal kidney function 4½ years post-liver transplantation. These results led Sanjad et al. (1999) to suggest that combined organ transplantation provided the best long-term results. Sanjad et al. (1999) found that PHI accounted for 20% of all cases of nephrocalcinosis diagnosed during the corresponding study period and 6% of end-stage renal disease, leading Sanjad et al. (1999) to conclude that PHI may be a more frequent cause of nephrocalcinosis and end-stage renal disease in Saudi Arabia than previously recognized probably due to a high rate of consanguineous marriages.

Qatar

Ehlayel and Akl (1992) reviewed the records of all patients in Qatar diagnosed with chronic renal failure between the years 1982 and 1990. Of the total of 30 such cases, one patient was found to have been diagnosed with hereditary oxalosis.

United Arab Emirates

[See: Oman > Hauggaard and Ekelund, 2000].

References

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- Ehlayel MS, Akl KF. Childhood chronic renal failure in Qatar. *Br J Clin Pract.* 1992; 46(1):19-20. PMID: 1419547
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- Sanjad SA, Al-Abbad A, Al-Sabban E. Primary hyperoxaluria type 1: An underestimated cause of nephrocalcinosis and chronic renal failure in Saudi Arabian children. *Ann Saudi Med.* 1999; 19(1):4-7. PMID: 17337975

Related CTGA Records

Alanine-Glyoxylate Aminotransferase
Nephronophthisis 1
Polycystic Kidney Disease Autosomal Recessive

External Links

<http://ghr.nlm.nih.gov/gene=agxt>
<http://www.emedicine.com/med/topic3027.htm>
<http://www.genetests.org/profiles/ph1>
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=416

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