STUDY NOTES · BASIC CONCEPT

What is Primary hyperoxaluria (PH)?

Science & Technology

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What?

Primary hyperoxaluria (PH) is a rare group of inherited genetic metabolic disorders characterized by the overproduction of oxalate, a waste product normally excreted by the kidneys. This leads to high levels of oxalate in the urine (hyperoxaluria), causing recurrent kidney and bladder stones, nephrocalcinosis (calcium deposits in the kidneys), and potentially end-stage renal disease (ESRD). If untreated, excess oxalate can deposit in other organs (systemic oxalosis), affecting bones, heart, skin, and eyes.

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Types

There are three main types of PH, distinguished by the deficient enzyme and genetic cause:

- Type 1 (PH1): The most common (70-80% of cases) and severe form, caused by deficiency of alanine-glyoxylate aminotransferase (AGT) in liver peroxisomes. Encoded by the AGXT gene.
- Type 2 (PH2): Accounts for about 10% of cases, due to deficiency of glyoxylate reductase/hydroxypyruvate reductase (GRHPR). Encoded by the GRHPR gene. Less severe than PH1 but can still lead to ESRD.
- Type 3 (PH3): Also about 10% of cases, caused by deficiency of 4-hydroxy-2-oxoglutarate aldolase (HOGA). Encoded by the HOGA1 gene. Often milder, with symptoms sometimes resolving in adulthood.

All types are inherited in an autosomal recessive pattern, meaning both parents must carry the mutated gene, and affected individuals inherit two copies.CausesPH results from mutations in genes that encode enzymes involved in glyoxylate metabolism in the liver (primarily for PH1 and PH2) or liver and kidneys (PH3). These

mutations lead to reduced enzyme activity, causing glyoxylate to accumulate and convert to oxalate instead of glycine or other harmless products.

Oxalate binds with calcium to form insoluble crystals, damaging the kidneys. Over 200 mutations have been identified in AGXT for PH1 alone.FrequencyPH affects approximately 1 in 58,000 people worldwide, with PH1 being the most prevalent. It occurs equally in males and females and can present at any age, though PH1 often manifests in childhood.

Symptoms

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Symptoms vary by type and severity but primarily affect the kidneys:

- Recurrent kidney stones (urolithiasis) starting in infancy or childhood.
- Blood in urine (hematuria), abdominal pain, urinary tract infections.
- Nephrocalcinosis and progressive kidney damage leading to chronic kidney disease (CKD) and ESRD.
- In advanced stages, systemic oxalosis: Bone pain/fractures, heart arrhythmias, skin nodules, vision problems (retinopathy), anemia, and nerve damage. PH1 can be fatal if untreated, with infantile forms causing rapid kidney failure.

Diagnosis

- Urine Tests: 24-hour urine collection showing elevated oxalate (>0.5 mmol/1.73 m^2/day) and often glycolate (PH1) or L-glyceric acid (PH2).
- Blood Tests: Plasma oxalate levels, kidney function (eGFR).
- Imaging: Ultrasound or CT for stones/nephrocalcinosis.
- Genetic Testing: Confirms mutations in AGXT, GRHPR, or HOGA1.

- Enzyme Assays: Liver biopsy to measure enzyme activity (rarely needed now due to genetic testing). Early diagnosis is crucial, often prompted by recurrent stones in young patients.

Treatment

Treatment aims to reduce oxalate production, prevent stone formation, and manage complications:

- Conservative Measures: High fluid intake (>3 L/day), low-oxalate diet, potassium citrate or orthophosphate to inhibit crystal formation.
- Medications: Vitamin B6 (pyridoxine) for responsive PH1 cases (up to 30% benefit by reducing oxalate). RNA interference (RNAi) therapies like lumasiran (Oxlumo®) for PH1, which inhibits glycolate oxidase to lower oxalate production; approved for all ages.
- Dialysis: For ESRD, but ineffective at removing all oxalate; often combined with transplantation.
- Organ Transplantation: Combined liver-kidney transplant is curative for PH1, as the liver produces the missing enzyme. Isolated kidney transplant may suffice for milder cases or post-liver transplant. Living donor options, like mono-segment liver transplants, are used in pediatrics. Success rates are high with early intervention, but lifelong monitoring is needed.

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Prognosis

With early diagnosis and treatment, prognosis has improved significantly. Untreated PH1 often leads to ESRD by age 20-30, with 50% mortality by age 40. Modern therapies like RNAi and transplants offer better outcomes, especially for children. Regular follow-up is essential to prevent complications.Research and SupportOngoing research focuses on gene therapies, enzyme replacement, and novel inhibitors. Patient registries like the Oxalosis and Hyperoxaluria Foundation aid in data collection. Genetic counseling is recommended for families.