Primary Hyperoxaluria Type 1 Backgrounder

Disease Overview

Primary hyperoxaluria (PH) constitutes a group of rare inherited disorders of the liver characterized by the overproduction of oxalate, an end product of metabolism. Oxalate cannot be broken down by the human body and, when at high levels, it accumulates and can cause irreparable damage to the kidneys.[1,2]

There are 3 types of PH: type 1 (PH1), type 2 (PH2), and type 3 (PH3). PH1 is the most common and severe form, accounting for 70% to 80% of all cases. PH1 affects 1 to 3 individuals per million in the United States and Europe, and has a higher prevalence in some regions, such as the Middle East and North Africa.[1,3]

Symptoms

People with PH1 often present with nephrocalcinosis (accumulation of excess calcium oxalate in the kidneys) and oxalate stones throughout the urinary tract and kidneys. When a person with PH1 has a kidney stone, symptoms can include flank pain, urinary tract infections, painful urination, and blood in the urine.[4]

PH1 Manifestations by Stage of Life	
Infancy	**Childhood/Adolescence/Adulthood**
Insufficient weight gain	Recurrent kidney stones with family history of stones
Formation of kidney stones	Progressive kidney disease (including kidney failure)
Early end-stage renal failure	Multi-organ dysfunction due to buildup of oxalate

Over time, kidney function declines so that the kidneys can no longer excrete as much oxalate as they receive. This can often result in end-stage renal disease (ESRD), a life-threatening condition that prevents the kidneys from filtering fluids and waste from the body effectively. As a result, oxalate levels in the blood rise and it begins to accumulate and deposit elsewhere in the body, including eyes, bones, skin and heart, causing diminished vision, bone fractures, ulcers, and heart failure.[4] Complications associated with ESRD and/or widespread deposition of oxalate, referred to as systemic oxalosis, can be fatal.[2,4]

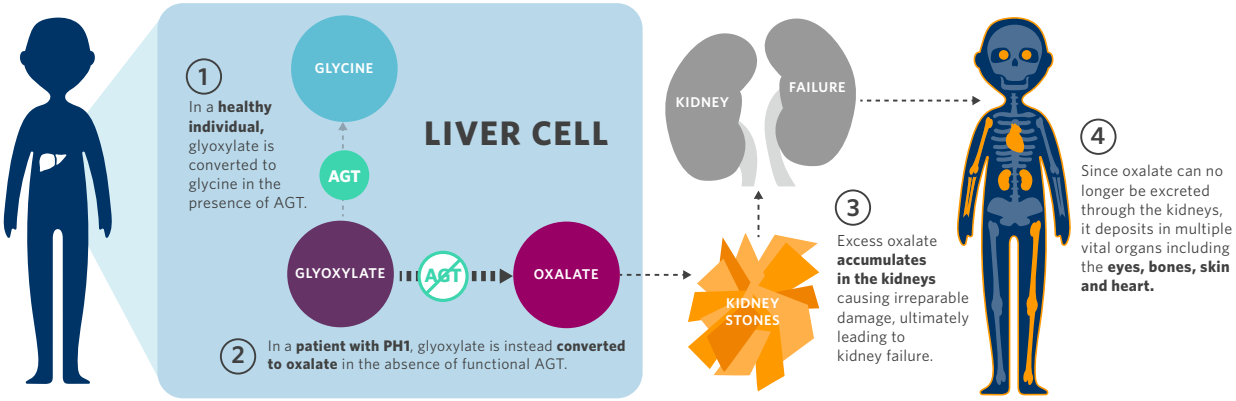
Diagnosis

Patients can be diagnosed with PH1 at any age, but many individuals experience their first symptoms in early childhood. For many patients, PH1 is not diagnosed immediately. Since kidney stones in adults are more commonplace, adult patients with PH1 often spend many years undiagnosed until they present with severe kidney disease. Some individuals are not diagnosed until after their kidneys have failed and they require dialysis to help filter waste products from the blood.[4]

Since PH1 is an inherited condition, genetic testing can be used to confirm a diagnosis.

Cause

PH1 is caused by a genetic defect in a liver enzyme called alanine-glyoxylate aminotransferase, or AGT.[1] AGT, when functional, helps rid the body of unwanted products of normal metabolism. In people with PH1, defective AGT causes an abnormal accumulation of oxalate, initially in the kidneys, and, when the disease advances, in other vital organs of the body.



Management and Treatment

Current management options include hyperhydration, high dose vitamin B6 therapy, and calcium oxalate crystallization inhibitors. Very few PH1 patients are complete responders to vitamin B6 therapy and a subset of patients show a partial response, although data are limited. Patients with advanced disease require dialysis as a bridge to a dual liver/kidney transplant, which resolves the metabolic defect in the liver and replaces the terminally damaged kidneys.[1,2]

For more information on primary hyperoxaluria type 1, visit Alnylam.com/patients/primary-hyperoxaluria.

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4. Milliner DS et al. *GeneReviews®*; [updated Nov 30, 2017]. https://www.ncbi.nlm.nih.gov/books/NBK1283/.