Cystinuria

Cystinuria is an autosomal recessive disease caused by a defect of an amino acid transporter in the proximal tubule of kidneys. This defect prevents proper reabsorption of basic, or positively charged amino acids, including cystine, ornithine, lysine and arginine. Inability to reabsorb these amino acids causes them to become concentrated in the urine. Cystine is a dimer formed by a sulfide bond between two cysteine amino acids. Accumulation of cystine in the urine can precipitate out, resulting in kidney stones. Cystine crystals form hexagonal-shaped crystals, and can be seen under microscopic analysis of the urine. These crystals can enlarge to form staghorn kidney stones as well. If not treated properly, the disease can cause serious damage to the kidneys. Stones can be identified by a positive nitroprusside test. Initial treatment is adequate hydration and alkalization of the urine with acetazolamide, because the cystine stones are more likely to precipitate in acidic urine. However, once large renal stones have formed, surgery may be required to remove them.



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Pathophysiology

Autosomal Recessive
Recessive-chocolate
Cystinuria is inherited in an autosomal recessive manner.

Defect of Renal Tubular Amino Acid Transporter
Kidney-tuba with A-mean-ol' Acidic-lemon Transporter
The primary pathophysiologic mechanism underlying cystinuria is a defective amino acid transporter in the proximal tubules of the nephrons in the kidneys. This defect arises from genetic mutations in the SLC3A1 and/or SLC7A9 genes. As a result, the reabsorption of basic, positively charged amino acids is impaired, leading to high levels of these amino acids in the urine.

C-O-L-A Acronym
Cola
COLA is an acronym for the amino acids that are unable to be reabsorbed in this disease: (dibasic) cystine, ornithine, lysine, and arginine.

Cystine
Sistine (Chapel)
Cystine is not technically an amino acid, it is a dimer of cysteine molecules linked by a disulfide bond. In this dibasic form, cystine is poorly soluble in urine and may precipitate, forming cystine stones in individuals with cystinuria.

Ornithine
Hornet
Ornithine is an amino acid involved in important biochemical pathways in the body, including the urea cycle. However, it is not typically incorporated into proteins. In cystinuria, ornithine is not reabsorbed in the kidney's proximal tubule, leading to its presence in the urine.

Lysine
L-icing
Lysine is a basic amino acid that is not properly reabsorbed due to a defect in the kidney transporter in individuals with cystinuria.

Arginine
Argentina-flag
Arginine is a basic amino acid that is not properly reabsorbed due to a defect in the kidney transporter in individuals with cystinuria.

Signs and Symptoms

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Excess Cystine in Urine

Crystals in Urine

Cystine can precipitate out of urine due to its poor solubility and form kidney stones (nephrolithiasis) in individuals with cystinuria. This can lead to classical kidney stone symptoms, such as flank pain, often associated with renal colic. It is characterized by a severe, sudden onset of sharp pain that radiates from the flank to the lower abdomen or groin. It may also cause hematuria, nausea, vomiting, and urinary urgency or frequency as the stone moves through the urinary tract.

Hexagonal Crystals

Hexagonal Crystal

Staghorn kidney stones are large stones in the upper urinary tract that occupy the renal pelvis and extend into at least two of the calyces. While all types of urinary stones can form staghorn calculi, the majority are composed of a struvite-carbonate-apatite matrix, commonly due to urease-producing urinary tract infections such as Proteus mirabilis, which is known to produce urease. In patients with cystinuria, extensive precipitation of cystine out of the urine can also lead to the formation of staghorn calculi.

Staghorn Kidney Stones

Stag with Staghorn Kidney Stones

Staghorn kidney stones are upper urinary tract stones that involve the renal pelvis and extend into at least two of the calyces. All types of urinary stones can potentially form staghorn calculi, but the majority are composed of struvite-carbonate-apatite matrix. Patients with cystinuria can form staghorn calculi due to extensive precipitation of cystine out of the urine.

Urinary Tract Infections

Urinary-tract-on-fire

Recurrent urinary tract infections (UTIs) in cystinuria occur due to the alkaline environment created by the precipitation of cystine in the urine. Urine stasis created by this environment is ideal for bacteria to thrive. Also, cystine stones can irritate the urinary tract, making it more susceptible to infections.

Diagnosis

Cyanide Nitroprusside Test

Sai Nitro-puss

The cyanide nitroprusside test is a urinalysis test used to detect cystine in the urine. In this test, cyanide nitroprusside is added to the urine, and a purple color develops if cystine is present. The cyanide nitroprusside reagent reacts with the disulfide bonds in cystine, resulting in a color change that indicates the presence of cystine in the urine.

Treatment

Hydration

Hydrating with water

High fluid intake (>3 L/day) to dilute urine. Good hydration is a universal management and prevention of kidney stones.

Alkalinize the Urine

Up-arrow Alkaline pH-strip

Acidic urine favors cystine precipitation; therefore, alkalinizing the urine is a key component of treatment to prevent stone formation in cystinuria. For alkalizing agents, potassium citrate, which is the preferred drug of choice, and acetazolamide in selected cases are used.

Penicillamine

Pencil-mine

Penicillamine treats cystinuria by acting as a chelating agent that binds to cystine in the urine and forms a soluble complex. Penicillamine-cysteine disulfide is much more water-soluble than cystine. This reduces the precipitation of cystine and prevents the formation of kidney stones.

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