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REVIEW OF CYSTINURIA

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ABSTRACT

Cystinuria is a primary inherited aminoaciduria caused by mutations in the genes that encode the two subunits (neutral and basic amino acid transport protein rBAT and b(0,+)-type amino acid transporter 1) of the amino acid transport system b0,+. This autosomal recessive disorder (in which few cases show dominant inheritance) causes a failure in the reabsorption of filtered cystine and dibasic amino acids in the proximal tubule. The loss of poorly soluble cystine, which precipitates to form stones, is what causes the disease's clinical symptoms. While cystinuria is uncommon, its frequency is high enough for the condition to significantly contribute to juvenile renal lithiasis, despite its rarity. A new classification of cystinuria and the awareness that certain cases result in stones have been made possible by a detailed understanding of cystine transport mechanisms during the past 15 years and the genetic defects responsible for the condition. While cystinuria is uncommon, its frequency is high enough for the condition to significantly contribute to juvenile renal lithiasis, despite its rarity.

KEYWORDS

Cystinuria, kidney stones, nephrolithiasis, chronic kidney disese, nephrology, urology.

INTRODUCTION

Cystinuria is an inherited disorder of renal amino acid transport that causes recurrent nephrolithiasis and significant morbidity in humans. It has an incidence of 1 in 7000 worldwide making it one of the most common genetic disorders in man. Cystinuria is caused by an inherited defect in the transport of cystine and dibasic amino acids (ornithine, lysine, and arginine) in renal tubular cells. Cystine is not soluble in urine so kidney and bladder stones form when the renal tubule fails to reabsorb the amino acid back into the bloodstream. Recurrent cystine kidney stones are associated with pain, frequent urinary tract infections, bleeding, urinary tract obstruction, need for multiple surgical procedures, and kidney failure. Medical treatment to prevent the formation of cystine stones is not very effective and has many unpleasant side effects.[1]

CLASSIFICATION

Cystinuria is typically regarded as an autosomal recessive disease. Based on the urine excretion of cystine and dibasic (lysine, arginine, and ornithine) amino acids of the heterozygous parent, three cystinuria phenotypes—type I type ii, and type iii2—have historically been defined[2]. Whereas obligate heterozygotic relatives of people with type I cystinuria have normal aminoaciduria, those with type ii and type iii cystinuria have severe or moderate hyperexcretion of cystine and dibasic amino acids, respectively.

EPIDEMOLOGY

The condition affects roughly 1:7,000 people worldwide, however there are substantial ethnic variations. Particularly among Libyan Jews, the disease occurs more frequently than in the Swedish population (1:100,000).About 1%–2% of adult and 6%–8% of paediatric stone cases are cystine-related [3]. Boys typically present earlier than girls, with the average age of clinical presentation being around 12 years[4].

PATHOPHYSIOLOGY

Cystine is a homo-dimer of the amino acid cysteine. Cystine transport occurs within the proximal tubule of the nephron and its transepithelial transporter is also responsible for the transport of the dibasic amino acids ornithine, lysine, and arginine (COLA). This transporter is also found within the gastrointestinal (GI) tract, though this aspect has no known significance with regard to pathology of the disease[5].The transporter consists of two subunits linked by a disulfide bond, and b0,+AT1 and functions by binding to the dibasic molecule cystine within the lumen of the proximal tubule where it is then reduced to individual cysteine molecules before returning to the bloodstream[6].This transporter has a genetic flaw that leads to cystinuria. SLC3A1 and SLC7A9 have two known mutations, while up to 5% of individuals do not have a known mutation [7]. Recent research in mice has revealed a novel transporter called AGT1 to be involved in the transport of cystine, which may help to explain unexplained mutations in humans that cause cystinuria [6]. rBAT is encoded by SLC3A1[8]. Type A cystinuria is the condition present in patients with this mutation. While a substitution mutation that causes faulty transport of the transporter to the membrane is the most frequent alteration. B0,+AT1 is the other component that is encoded by SLC7A9 [9]. Type B cystinuria is the diagnosis for individuals carrying this mutation. 133 and 95 SLC3A1 mutations, respectively[10].

SYMPTOMS

Cystine stones can cause systemic symptoms like nausea and vomiting as well as flank discomfort that radiates to the groyne[11]. They can also cause hematuria and dysuria[12].

DIAGNOSIS

Intravenous pyelogram

An X-ray examination of the kidneys, bladder, and ureters, uses a dye in the bloodstream to help see the stones[13].

Abdominal CT scan

Uses X-rays to create images of the structures inside the abdomen to look for stones inside the kidneys[14].

Urinalysis

It may involve looking at the color and physical appearance of the urine, viewing the urine under a microscope, and conducting chemical tests to detect certain substances, such as cystine[15].

COMPLICATION

If not treated properly, cystinuria can be extremely painful and may lead to serious complications. These complications include:

- kidney or bladder damage from a stone
- Ureteral obstruction, a blockage of the ureter, the tube that drains urine from the kidneys into the bladder
- Urinary tract infection
- Kidney infection

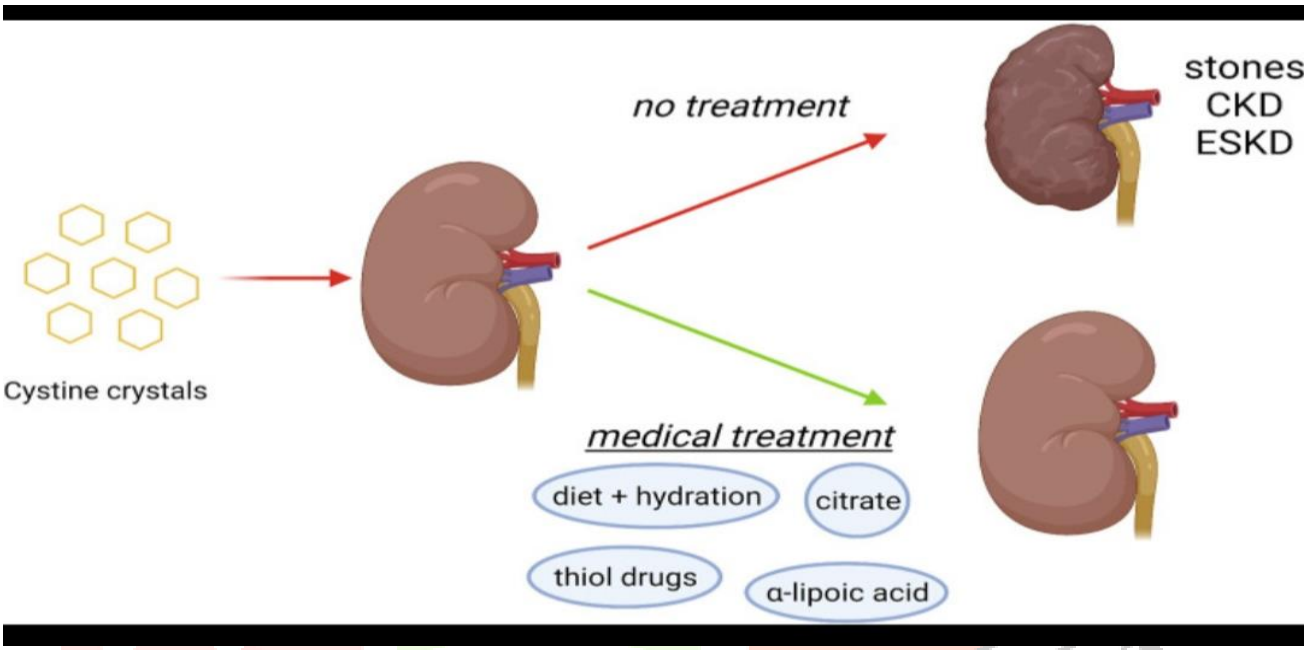

Figure 1 : Complication of cystinuria

TREATMENT

Alkalizing agents

The pH is an important factor for kidney stones to form, as cystine is more soluble at a higher pH[16]. For this reason, alkalizing agents like potassium citrate can help to increase the pH and the solubility of cystine, resulting in fewer recurrences.

Chelation or antiurolithic therapy

Thiol compounds

Thiol compounds have the ability to bind to cystine, which results in the formation of a disulfide complex that does not cause stones to develop and may instead help to dissolve kidney stones[17].

D-penicillamine

D-penicillamine is a chelating agent that increases the solubility of cystine, reducing the effects of cystinuria[18]. Approximately half of all patients experience adverse reactions with this therapy, which limits its therapeutic use. These effects may include rash, gastrointestinal effects, arthralgia, leukopenia, and nephritic syndrome.

Tiopronin is another agent with similar action and side effect profile.

Alpha-mercaptopropionylglycine (alpha-MPG) is a second-generation chelating agent with a similar mechanism of action, but is generally tolerated better that C-penicillamine.

Captopril

Captopril, which is an angiotensin-converting enzyme (ACE) inhibitor drug that is typically used to treat hypertension, forms a thiol-cystine mixed disulfide, which has a higher solubility and can reduce the formation of stones[19]. This is usually used a second-line therapy option when other treatments have failed to produce an adequate response.

Surgical procedures

When the stones in the urinary tract are large in size and cause significant p ain, their surgical removal may be necessary to relieve symptoms[20]. There are several different surgical procedures that may be performed, depending on the specific circumstances.

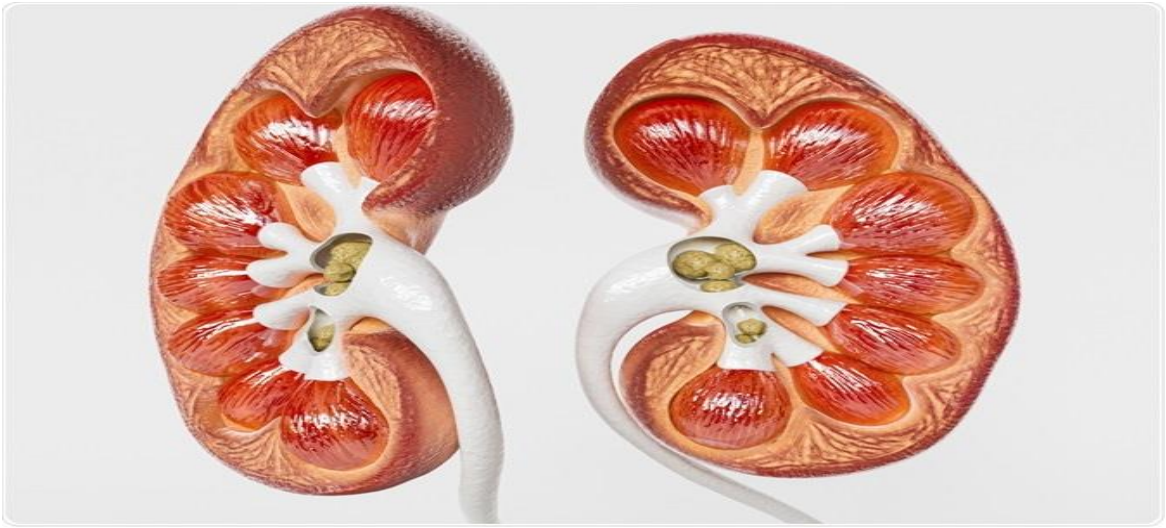

Figure 2:Surgery

Extracorporeal shock wave lithotripsy (ESWL)

Extracorporeal shock wave lithotripsy (ESWL) uses shockwaves directed towards large stones to fragment the stones into smaller pieces that can pass through the ureters and be excreted more easily[21]. However, this procedure is less effective for kidney stones associated with cystinuria than other types of stones[22]. Percutaneous nephrolithotomy

Percutaneous nephrolithotomy involves the insertion of an instrument into the kidney that is used to break the stones or remove them from the organ entirely[23].

CONCLUSION

Over the past 15 years, despite our growing understanding of the molecular causes of cystinuria, the care of patients has not much improved. Thorough characterization of the cystinuria-related molecular abnormalities may aid in the creation of novel therapeutic strategies. Consequently, small-chaperone therapy may be used to target mutations that result in protein misfolding[24]. Furthermore, genes not directly connected to the onset of the disease may influence how cystine stones form. Therefore, research using mice models of cystinuria may aid in locating the genes that control cystine lithiasis. To find such modulator genes in humans, a sizable cohort of individuals with cystinuria and well-characterized clinical and molecular aspects would be required.The therapy of cystinuria could then shift to targeting prolithiasis and antilithiasis proteins.

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