Cystinosis

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Abstract

Cystinosis, an autosomal recessive disease, is a metabolic disease characterized by an accumulation of cystine in different organs and tissues due to a defect of cystine transport out of lysosomes. The gene responsible for the disease, CTNS, is located on chromosome 17 and encodes for a lysosome-membrane protein, cystinosin. The first clinical signs appear three and six months of age, with polyuria, dehydration, rickets and retarded growth, secondary to impaired proximal tubular reabsorptive capacity, leading to the varied manifestations of the de Toni-Debré-Fanconi syndrome. The disease evolves progressively towards renal failure after 6 years of age. Cystine deposits in the cornea and conjunctiva cause tearing, and photophobia. Other organs are also affected later in life: hypothyroidism, insulin-dependent diabetes, hepatosplenomegaly with portal hypertension, muscle involvement, and cerebral involvement. The diagnosis of cystinosis is confirmed by determining the cystine content of leukocytes. A prenatal diagnosis can be obtained by genetic analyses or by measuring 35S-labeled cystine incorporation into fibroblasts cultured from amniotic fluid or chorionic villi. Treatment consists of water, electrolyte and vitamin D supplements; indomethacin, which improves the patient's general status and growth; and cysteamine, which lowers the leukocyte cystine concentration thereby slowing the progression to renal failure. The disease does not recur in the graft after renal transplantation.

Keywords
Cystinosis, cystine, autosomal recessive transmission, cysteamine, renal transplantation

Disease name and synonyms
Cystinosis

Definition
Cystinosis is a metabolic disease characterized by an accumulation of cystine in different organs and tissues, leading to potentially severe organ dysfunction. Three forms of cystinosis have been...
described: infantile (nephropathic), intermediate (adolescent, late-onset) and adult (benign).

**Incidence**

Nephropathic cystinosis, which is the most common form, has been estimated to affect one out of every 100,000 to 200,000 children [1,2].

**Clinical description**

**Infantile cystinosis**

Cystinosis is characterized by both renal and extrarenal symptoms.

**Renal symptoms**

The first clinical signs of infantile cystinosis appear between 3 and 6 months of age; they are largely due to impaired proximal tubule reabsorption capacity, leading to the varied manifestations of the de Toni-Debré-Fanconi syndrome. Excessive sodium and water excretion can result in polyuria (reaching 2-3 L/day), polydipsia, vomiting, unexplained fever and acute dehydration episodes. Growth retardation and rickets are often noted at presentation due in part, to phosphate loss and hypophosphatemia. Other common abnormalities include glucosuria, tubular proteinuria (with generalized amino aciduria), proximal renal tubule acidosis (manifested by a hyperchloremic [normal anion gap] acidosis), hypokalemia and hypouricemia [3]. The tubular losses gradually become less prominent after age 6 years due to a progressive decline in the glomerular filtration rate. End-stage renal failure typically occurs before 10 years of age. Histological examination of cystinotic kidney biopsies shows nonspecific tubular and glomerular lesions. The proximal and distal tubules are dilated or atrophic and vacuoles may be seen in the tubule cells. Interstitial fibrosis and glomerulosclerosis are seen in advanced disease.

**Extrarenal symptoms**

Growth retardation is a major feature of cystinotic patients. The mean adult height is only 54 inches (136.5 cm) for males and 49 inches (124 cm) for females. Growth curves have improved in recent years due to early therapy with fluid and electrolyte supplements, indomethacin, and cysteamine. Puberty is usually delayed. The extrarenal symptoms are due to the intracellular accumulation of cystine in different tissues and organs [4]. The eyes are involved early during the course of the disease, as cystine deposits in the cornea and the conjunctiva can be seen on slit-lamp examination. These deposits are responsible for photophobia, tearing, and blepharospasms. Irregular and peripheral depigmentation of the retina is also an early finding. Visual impairment may occur children over 10 years old [5]. Hepatomegaly, resulting from enlarged Kupffer cells with cystine crystals, occurs in 40% of the patients and may lead to portal hypertension. Splenomegaly, due to enlarged cells in the red pulp, can also be seen. Hypothyroidism is also common in older children. It can be detected by the demonstration of high plasma TSH (thyroid stimulating hormone) levels, which occur before the thyroxine concentration begins to fall [6]. Symptoms of hypothyroidism are uncommon, but this disorder may contribute to impaired growth. Insulin-dependent diabetes has been reported, primarily in cystinotic patients on peritoneal dialysis or after kidney transplantation when high doses of corticosteroids are given to treat acute rejection [7]. The hyperglycemia is usually transient, although a few patients require chronic insulin therapy [8]. Exocrine pancreatic insufficiency with steatorrhea has been reported in one patient [9]. Muscular weakness is observed early in the course of the disease. It is due initially to hypokalemia and to carnitine deficiency. Older children may develop a myopathy secondary to cystine crystal accumulation in the muscle cells [10].

Low plasma testosterone levels and incomplete pubertal development is a common finding in older boys [11]. This complication, which may persist after renal transplantation, reflects testicular disease induced at least in part by cystine deposition, since pituitary function appears to be intact [11]. Central nervous system involvement is a late complication that occurs after age 20 years of age [12-14]. The main symptoms are difficulty in walking and swallowing, progressive loss of speech, and diminished intellectual function. Pyramidal signs and cranial nerve defects also may be seen.

**Intermediate cystinosis**

The clinical course is more indolent than in the other forms of cystinosis. The first symptoms of adolescent cystinosis typically appear around 8 years of age. The manifestations of Fanconi’s syndrome are less severe and end-stage renal disease occurs after the age of 15 years [15,42].

**Adult cystinosis**

Adults with cystinosis are generally asymptomatic. They may suffer from photophobia, with the diagnosis being made.
after observation of corneal crystal deposits by the ophthalmologist. [41]

**Treatment**

Therapy of cystinosis consists of attenuation of symptoms, the administration of cysteamine and renal transplantation for those who progress to end-stage renal disease.

**Symptomatic therapy**

The initial aim of the symptomatic treatment of infantile cystinosis is to replace the fluid and electrolyte losses induced by proximal tubule dysfunction. Water intake has to be adjusted according to urine output and should be increased during episodes of fever. Sodium and potassium bicarbonate supplements are given to maintain the plasma bicarbonate concentration between 21 and 24 meq/L and to correct hypokalemia. Some patients require as much as 10-15 mEq/kg of bicarbonate/day, because raising the plasma bicarbonate concentration above the reduced tubule reabsorption capacity results in the rapid excretion of the exogenous bicarbonate in the urine.

Tubular losses of water, sodium and potassium may be drastically reduced by indomethacin at a dose of 1-3 mg/day [16]. This regimen frequently allows tube feeding, which is necessary in most patients, to be discontinued. It also improves appetite and growth. Fluid and electrolyte losses, and therefore the need for supplementation also diminish with age due to the progressive decline of the glomerular filtration rate.

Other supplements are also required in affected children. These include phosphate (1-3 g/day) to maintain the plasma phosphate level above 3.7 mg/dL (1.2 mmol/L) and calcium, magnesium, and vitamin D, to prevent rickets. Vitamin D can be given as 10-25 µg/day of calcidiol (25-hydroxyvitamin D) or at a starting dose of 0.25 µg/day of calcitriol (1,25 dihydroxyvitamin D). The vitamin D dose should be adjusted according to the plasma calcium concentration. L-Carnitine supplementation is recommended, with a starting dose of 50-100 mg/kg/day titrated to maintain plasma carnitine levels within the normal range [17]. Thyroxine replacement is indicated for children whose levothyroxine levels are below 9 pmol/L, with or without high TSH levels. Growth-hormone therapy is safe and effective. Treatment should be started early during the course of the disease when adequate nutrition and cysteamine treatment do not prevent growth retardation. [18].

**Cysteamine**

Cysteamine administration of directly treats the disease by reducing the intracellular cystine content. Cysteamine enters the cell and accumulates in lysosomes, where it reacts with cystine to form both cysteine and cysteine-cysteamine complexes that are able to leave the lysosomes. The cysteamine dose should be progressively increased from 10 to 50 mg/kg/day. The drug is rapidly absorbed and its effect lasts for only 6 hours. It should therefore be given every 6 hours to prevent intracellular cystine accumulation. Cysteamine should be started as soon as the diagnosis of cystinosis is confirmed [19]. Phosphocysteamine has the same effects as cysteamine but without the bad taste or smell [19]; an oral phosphocysteamine solution can be given every 12 hours [20]. Cysteamine bitartrate is available and patients seems to be more compliant with this formulation.

Cysteamine treatment has no effect on preexisting fluid and electrolyte losses. However, children treated adequately (as assessed by leukocytes depletion of cystine) and early show improved growth and maintenance of the glomerular filtration rate and are less likely to develop hypothyroidism [19,21]. Poorly compliant patients and those treated at an older age do not have as great benefit as much, although the rate of progression to renal failure is slowed [22]. Trials are in progress to determine whether cysteamine will prevent all of the extrarenal manifestations of cystinosis. Topical but not systemic cysteamine is effective in preventing corneal crystal deposition and in reducing photophobia [23, 43, 44].

**Renal transplantation**

There are no specific recommendations for the treatment of cystinotic patients with end-stage renal disease. In children, renal transplantation for cystinosis is more successful than for renal failure due to other [24,25]. This outcome may reflect diminished immune responsiveness induced by intracellular cystine accumulation [26]. Cystine-induced tubule dysfunction does not recur in the graft, although cystine does accumulate in the interstitial cells. However, there is considerable long-term morbidity from extrarenal cystinosis following renal transplantation [25]. In one study on 36 patients, for example, 31% were on thyroid hormone replacement therapy, 21 had moderate to severe swallowing abnormalities, 8 had cerebral calcifications, and 5 were blind. Few patients over the age of 20 years had no serious complications and those over the age of 30 were usually doing poorly, although many were still working. Lack of prolonged compliance with cysteamine therapy may have been a major
cause of these problems. It is estimated that depletion of excess cystine from muscle requires 4-11 years of therapy [25].

**Etiology**

Cystine is derived from protein degradation in cellular lysosomes. Free cystine is normally transported through the lysosomal membrane to the cytosol where it is reutilized after its transformation to cysteine. In cystinosis, cystine accumulates inside the lysosomes because of a defect in the transport system [27-31]. Cystine is poorly soluble and forms crystals as its concentration increases. Cystinosis is transmitted as an autosomal recessive trait. Two observations suggest that the same gene is involved in all forms of the disease. First, both the infantile and adolescent forms can occur in a given family. Second, complementation studies using somatic cell hybrids derived from fibroblasts from patients different types of cystinosis have shown the absence of correction of the metabolic defect [38]. It therefore appears that there is no genetic heterogeneity and that the differences in the clinical manifestations result from mutations occurring in a single gene (allelic mutation).

The gene for nephropathic cystinosis has been mapped to chromosome 17p13 and identified [33]. The cystine transport nephrotic syndrome gene, CTNS, encodes for a 367 amino-acid protein, cystinosin, which has 7 transmembrane domains and structural characteristics similar to those of a lysosome membrane protein. A large number of mutations have been described in patients with cystinosis, with the clinical phenotype segregating with specific defects [34-36]

**Infantile cystinosis**

Two large deletions (one of 9.5-16 kb, and one of approximately 65 kb), as well as other mutations that would result in missense or in-frame deletions, are associated with infantile cystinosis, the most severe phenotype (see below) [36]. Among patients with such defects in both alleles, these abnormalities may result in the loss of adequate protein function, including no protein synthesis with some mutations. The 65-kb deletion is the most frequent mutation found in the homozygous state, being observed in nearly one-third of the patients with cystinosis. This deletion is present in either the homozygous or heterozygous state in approximately 75% of patients of European origin [37]. By comparison, the 9.5-16 kb deletion has been observed in only a single family.

**Intermediate cystinosis**

Intermediate cystinosis is more indolent than the other forms of cystinosis (see below). This attenuation appears to be due to the inheritance of a mutation known to cause infantile disease in one allele (as above) and relatively less clinically severe mutation in the other, or the inheritance of a relatively less severe mutation(s) in both alleles [36,38].

**Adult cystinosis**

Adult or benign (or ocular nonnephropathic) cystinosis, which is characterized by the presence of corneal crystals and photophobia but no renal disease, has been associated with additional mutations [34,35]. Similar to intermediate cystinosis, this form may be due to the inheritance of different abnormal alleles, including the presence of a severe and a mild mutation, the latter of which do not adversely affect kidney function [35].

**Diagnostic methods**

The presence of cystinosis can be confirmed by determining the cystine content of peripheral blood leukocytes or fibroblasts [39]. The assay using the cystine binding protein is more sensitive and enables identification of heterozygous carriers. The intraleukocyte cystine content is 5-15 nmol of half-cystine/mg protein in the infantile form, 3-6 in the intermediate form, <1 in heterozygous carriers, and <0.2 in normal individuals [40]. The isolation and characterization of the suspect gene will eventually lead to the development of a genetic-based diagnostic assay. Although a polymerase chain reaction (PCR) based detection assay has been reported, such techniques are not routinely available, at present.

**Antenatal diagnosis**

During the first trimester, prenatal diagnosis can be established by measuring, directly or after culture, 35S-labeled cystine incorporation into fibroblasts from amniotic fluid or chorionic villi. Chorionic villous sampling and the cystine-binding protein assay can also be used for prenatal diagnosis. The identification of a mutation in a previously affected sibling may allow early prenatal diagnosis.

**References**

32. Pellett, OL, Smith, ML, Greene, AA, Schneider, JA. Lack of complementation in somatic cell hybrids between fibroblasts from...
patients with different forms of cystinosis. Proc Natl Acad Sci USA 1988; 85:3531.