Cystinosis, a short overview and treatments

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RESUMEN

La cistinosis es una enfermedad multisistémica que se hereda de forma autosómica recesiva y cuyo origen está en mutaciones en el gen *CTNS*, que se localiza en el brazo corto del cromosoma 17. El gen *CTNS* codifica la cistinosina, que es un transportador lisosomal de cistina. A causa de las mutaciones en el gen *CTNS*, el transporte lisosómico se altera y los cristales de cistina se acumulan en diversos órganos. En el norte de Europa y en América la mutación más frecuente es la deleción de 57 kb. Hasta la fecha se han descrito más de 200 mutaciones en todo el mundo. Los riñones son el órgano afectado mayoritaria y principalmente. El síndrome de Fanconi renal es el signo distintivo de la cistinosis nefropática infantil, que es la causa más habitual del síndrome de Fanconi renal en niños. Junto con el compromiso del túbulo proximal renal, eventualmente se aprecian afectación y proteinuria glomerulares. El diagnóstico y el tratamiento precoces son la clave para preservar las funciones renales. Sin tratamiento, los pacientes cistinóticos alcanzan la fase final de la enfermedad renal al término de la primera década. Por tanto, son fundamentales el diagnóstico precoz y que se inicie el tratamiento —y se siga adecuadamente— con cisteamina. Los resultados del trasplante renal son satisfactorios.

Palabras clave:

Cistinosis, gen *CTNS*, defectos genéticos, manifestaciones clínicas, tratamiento con cisteamina, tratamiento precoz.

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INTRODUCTION

Cystinosis is a rare autosomal recessive disease with an incidence of 0.5-1 per 100.000 people[1]. It is caused by mutations in the *CTNS* gene that encodes the lysosomal cystine transporter, cystinosin (*CTNS*), leading to an accumulation of cystine within the lysosome[1,2]. This accumulation results in the impairment of cellular function, which eventually leads to multi-organ dysfunction[3,4]. Thus, a defect in *CTNS* and the accompanying cystine accumulation constitute a key player in the pathogenesis of cystinosis, which is more complex than the resulting cystine accumulation. The *CTNS* gene affects many intracellular pathways such as the inflammatory and fibrotic pathways, autophagy, mTOR signaling, lysosomal biogenesis and vesicle trafficking which take place in pathogenesis[5-8].

Renal Fanconi syndrome is the hallmark of infantile nephropathic cystinosis, which is the most common cause of renal Fanconi syndrome in children[9]. This syndrome presents alongside proximal renal tubular acidosis, which is a generalized dysfunction of the proximal tubule, characterized by the presence of polyuria, glycosuria, phosphaturia, tubular proteinuria, growth retardation, and rickets. Glomerular involvement and progression to kidney failure eventually develop. The first affected site is the proximal tubular cells (PTCs)[5]. However, evidence from murine models suggests that differentiation (structural changes) in PTCs starts prior to the accumulation of cystine crystals in both PTCs and the interstitium, leading to a loss of PTC brush borders, flattening and thickening of the tubular basement membrane, and a subsequent development of the characteristic swan-neck deformity[5]. These tubular changes progress to tubular atrophy and, in addition, heavy inflammatory cell infiltrates can be observed in the renal interstitium. Glomerular involvement with multinucleated podocytes can be seen in renal biopsies and later focal segmental glomerulosclerosis (FSGS) lesions may appear[9].

To date, life-long cystine-depleting therapy with oral cysteamine, the only specific therapy for cystinosis, and the availability of renal replacement therapy in childhood has dramatically improved patient outcomes[2-4]. There is strong evidence that early initiation and continued appropriate therapy with cysteamine are essential for delaying the progression to chronic kidney disease (CKD) and end-organ damage[10].

GENETICS

Cystinosis is a rare autosomal recessive disease. The *CTNS* gene responsible for the disease is located on chromosome 17 and was first identified in 1998[11]. This gene consists of a total 12 exons and carries 23 kb of genomic DNA. The gene encodes the 367 amino acid cystinosin protein, which has 7 transmembrane domains. Research has identified more than 200 mutations in this gene (deletion, insertion, nonsense, missense and splice site) that cause cystinosis. The most common of these mutations is a 57 kb deletion, which includes the first nine exons of the *CTNS* gene and part of exon 10 along with two upstream genes (*CARKL* and *TRPV1*). It is the most common genetic defect for more than half of patients with cystinosis in Northern Europe and North America[12,13]. The frequency of the 57-kb deletion in patients with cystinosis is 22% in Mexico and 17% in Italy, whereas no cystinosis patients in Turkey and Egypt show this deletion[14-18].

Apart from this mutation, W138X and c.1015G>A (G339R) were also found to be founder mutations in French Canadians and the Amish community in southeastern Ontario[19,20]. The missense mutation c.1015G>A (G339R) is also frequently observed in cystinosis patients in northern and southern Italy, Spain, Turkey, and the Middle East[17,21]. Another possible founder mutation is c.971-12G>A, which has been identified in the black population of South Africa[22].

The unique identification of the c.681G>A (p.E227E) mutation, with variable frequencies in the Middle Eastern population, along with its absence in European and American populations, suggests the existence of a possible founder mutation in this area[14,15,18,23].

Various authors have investigated the impact of the different types of *CTNS* mutation, and it is thought that individuals who have severe mutations, such as the loss of function mutations on both alleles, develop severe infantile cystinosis, whereas individuals who are homozygous or compound heterozygous for milder mutations have milder forms of cystinosis[10,24]. Homozygosity for the 57-kb deletion is associated with an increased risk of morbidity and mortality[9]. However, recent studies have shown that whereas mutations have no significant impact on kidney function and progression to kidney failure, commencing cysteamine treatment as early as possible has a significant impact on the preservation of renal function[14,25,26].

CLINICAL AND LABORATORY FINDINGS

There are three defined clinical forms, according to age at onset of the disease and the severity of renal involvement[2].

Nephropathic infantile form

Most patients (95%) belong to this group. Patients with nephropathic infantile cystinosis are clinically completely normal at birth. Findings develop over time with the deposition of cystine crystals in the organs. The earliest signs are growth retardation and findings of renal Fanconi syndrome, which, when due to cystinosis, is essentially a proximal tubule defect. In renal Fanconi syndrome, patients may exhibit acidosis due to bicarbonate loss, hypokalemia due to electrolyte loss, hyponatremia, hypophosphatemia, hypocalcemia and hypomagnesemia. While asymptomatic proteinuria appears in the first few weeks of life, glucosuria, phosphaturia and urinary bicarbonate losses can occur in later months. Therefore, the diagnosis of cystinosis may be missed in the first months of life. However, by the time the patient is six months old, the renal Fanconi syndrome is usually fully established. Loss of amino acids, carnitine, glucose, and low molecular weight proteins appear in the urine. In addition to electrolyte and mineral losses, polyuria, recurrent episodes of dehydration and polydipsia are other findings that manifest. Urinary losses of phosphate and calcium lead to increased alkaline phosphatase levels and rickets. Hypocalcemia leads to painful tetany attacks and even seizures in some patients. Hypocalcemia and acidosis accelerate bone resorption by causing secondary hyperparathyroidism[1-3].

The height, weight and head circumference of pediatric patients with cystinosis are normal at birth. In follow-up, the height and weight percentiles start to decrease around 6-12 months of age, and growth retardation is often the first finding. By the age of one year, height falls to the 3rd percentile and, without treatment, progresses at 50-60% of normal. Hypophosphatemic rickets, acidosis, nutritional retardation, and metabolic bone disease due to cystine storage in the bone figure among the causes of growth retardation[1,26].

Children with cystinosis often lack appetite and tend to consume salty and spicy foods. Polydipsia is another factor that contributes to loss of appetite, nausea and vomiting. There may also be enuresis due to polyuria[1].

The results of renal function tests are usually normal up to the age of five, and creatinine rarely exceeds 1 mg/dl. As the patient progresses to early childhood, deterioration in kidney function tests becomes evident. Untreated patients usually reach end-stage kidney disease (ESKD) by the age of 10, but with early, appropriate treatment the progression of ESKD is delayed to~ 20-30 years of age[1-4].

Extrarenal findings develop at a higher rate in patients with infantile nephropathic cystinosis who do not receive cysteamine therapy in the early period or whose treatment compliance is poor. Corneal cystine deposition is the first extrarenal finding in all cystinosis patients. It causes blepharospasm and photophobia in childhood. Cystine crystals usually begin to appear after 6-12 months of age. While superficial punctate and filamentary keratopathy frequently appear in adolescents, band keratopathy, peripheral corneal neovascularization, and posterior synechia associated with iris thickening are more common among adult patients. Retinopathy can lead to retinal blindness in 10-15% of patients[1,2].

Primary hypogonadism is seen in 70% of male cystinosis patients. Although delayed puberty is observed in girls, fertility is usually preserved in female cystinosis patients. On the other hand, male patients are infertile due to azoospermia. Although some patients have intact spermatogenesis at testicular level, no male cystinosis patients experience natural fatherhood. Today, through percutaneous epididymal sperm aspiration (PESA) followed by intra-cytoplasmic sperm injection (ICSI), fatherhood has become possible for male cystinosis patients[27].

Central nervous system findings secondary to cystinosis may also appear. These include hypotonia, tremor, delayed speech, decreased gross/fine motor skills, idiopathic intracranial hypertension, neurocognitive dysfunction, behavioral problems, and encephalopathy[2].

Cystinosis patients may also show distal vacuolar myopathy. In this case, weakness in the distal muscles, which usually occurs after the age of 20, is expected. More than half of patients with myopathy also have dysphagia[1,2]. Improved muscle function is a goal in patients with cystinosis.

DIAGNOSTIC METHODS

The early initiation of treatment for cystinosis has a major effect on the prognosis of this disease, hence the great importance of early diagnosis. There are three basic diagnostic methods for cystinosis, the first of which, genetic testing, constitutes an excellent and reliable diagnostic tool.

The second diagnostic method is leukocyte cystine level (LCL) measurement with high performance liquid chromatography (HPLC) or liquid chromatography-tandem mass spectrometry (LC-MS) /MS). LCL: 3-20 nmol/half-cystine/mg protein in patients with newly diagnosed cystinosis, <0.2 nmol/half-cystine/mg in the normal population, and <1 nmol/half-cystine/mg in heterozygous CTNS carriers[2,28].

The third method is demonstration of corneal cystine crystals, which is cheaper than the other two methods. It is usually possible to see cystine crystals in the eye after the age of one year, but an experienced ophthalmologist can identify cystine crystals at an even earlier age[1,2].

Nevertheless, physicians currently seek prenatal testing and preimplantation genetic diagnosis. Early diagnosis in newborns is very valuable, and the screening of neonates can be a point of interest, as the German a pilot study shows[29].

TREATMENT OF CYSTINOSIS

Symptomatic treatment

The aim of symptomatic treatment can be summarized as the provision of adequate fluid-electrolyte replacement and nutritional support, prevention of the development of rickets, and application of the necessary hormone replacement. A high-calorie diet should be recommended to prevent growth retardation. Nutritional support can be provided with a nasogastric tube in patients with significant anorexia. Access to water should not be restricted due to the fact that patients have polyuria. Oral sodium, potassium, phosphorus, sodium bicarbonate or sodium/potassium citrate can be used for electrolyte supplementation. Active vitamin D can be started from early childhood. If polyuria and polydipsia are very prominent, indomethacin may be given. However, renal function tests should be closely monitored when this treatment is started. Commencing angiotensin-converting enzyme inhibitors (ACEI) for glomerular proteinuria is controversial and, if started, there should be close monitoring with renal function tests. Furthermore, indomethacin and ACEI should not be used together. Endocrinopathy appears in many organs due to crystal deposition in cystinosis patients. In childhood, there should be close monitoring with thyroid and pancreatic function tests and replacement when necessary. Children who do not grow to a sufficient height despite appropriate food intake and cystine depletion therapy can undergo growth hormone replacement[1,2].

Cystine depletion

Currently, the only targeted therapy in the treatment of cystinosis is cysteamine therapy. Early diagnosis of cystinosis enables treatment with the only specific therapy for the disease, cysteamine, which should be administered as early as possible and continued lifelong[2]. It is well known that early treatment with cysteamine improves patient outcome, delays progression to renal failure and prevents or attenuates end-organ damage[9,14,25,26,30,31].

Initiation of cysteamine before two years of age has been associated with preservation of renal function in patients with cystinosis[10,25,31-35]. In the light of these studies, patient age at initiation of cysteamine therapy appears to be a major predictive factor of renal survival. In a large international current cohort of 453 patients with cystinosis, cysteamine was initiated in 89% of patients at a median age of 1.6 years, finding a near linear relationship between the age of cysteamine initiation and renal function[25]. Furthermore, patients treated before the age of one year exhibited the best renal outcome.

Two cysteamine bitartrate preparations are available on the market. One is short-acting and the other is long-acting. The short-acting drug was approved for the treatment of cystinosis in the United States in 1994 and in Europe in 1997[1]. In recent years, the recommendation is to use body surface area for drug dose calculation. Studies report that the target dose should be calculated as 1.3 g/m^2/day (maximum 1.95 g/m^2/day)[1,2].

The major side effects associated with drug intake are nausea, vomiting, epigastric pain and increased gastric acid secretion. For this reason, the initial starting dose is one sixth of the target dose and the dosage gradually

increases. If necessary, a proton pump inhibitor may also be given1. Apart from gastric hypersecretion, other side effects include hyperthermia, lethargy, neutropenia, seizures, and allergic rash. These side effects are usually reversible[36,37]. Some patients have reported skin striae, bone pain, myalgia, and endothelial proliferative lesions on the elbows when receiving high dose cysteamine therapy (>1.95 g/m^2/day)[36].

Apart from the short-acting cysteamine bitartrate administered four times a day, the American Drug Administration and the European Medicine Agency have approved a long-acting cysteamine preparation used twice a day. This new enteric-coated preparation opens in the small intestine, resulting in a higher plasma concentration. Comparative efficacy studies have shown that it is not inferior to the short-acting cysteamine bitartrate, and is an effective treatment[25,26].

However, oral cysteamine treatment has no effect on renal Fanconi syndrome, male infertility or corneal cystine accumulation. Therefore, recommendations are the frequent use of eye drops containing cysteamine during the day to prevent corneal cystine accumulation[1,2].

Progressive renal failure develops in most patients with nephropathic cystinosis[9]. Renal transplantation is the best therapeutic option for end-stage renal disease and improves both survival rate and quality of life[38]. Renal transplantation markedly improves the lifespan of patients with cystinosis, although cystine accumulation continues in non-renal organs[32]. While Fanconi syndrome does not recur in the transplanted organ, cysteamine therapy needs be continued for the patient's lifetime to prevent extrarenal complications. Cysteamine intake commences just after transplantation when the patient is able to take oral medication.

Aside from time of diagnosis, another critical factor for preservation of renal function is adherence to cysteamine therapy[36,37,39]. While evaluating the response to the drug, leukocyte cystine level is monitored. Cystine crystals accumulate in polymorphonuclear leukocytes rather than lymphocytes. Therefore, polymorphonuclear leukocytes are isolated instead of lymphocytes. However, polymorphonuclear leukocyte life is very short (approximately 12 hours), requires a large amount of blood, and cannot be performed everywhere due to technical difficulties[1,2].

Other potential monitors of therapy are inflammatory markers of macrophage activation such as IL-1β, IL-6, IL18, or chitotriosidase[8]. However, these inflammatory markers are not specific to cystinosis. Therefore, the development of alternative and selective diagnosis and monitoring strategies such as comprehensive screening of the entire genome, proteome, and metabolome may reveal more specific markers.

THE FUTURE TREATMENT MODALITIES

The first allogeneic hematopoietic stem cell therapy (HSCT) for cystinosis was performed in 2018; although there was some initial clinical improvement, the patient died due to multidrug-resistant sepsi[s40]. Some authors have presented autologous HSPC transplantation and a pharmacological treatment -Geneticin- of nephropathic cystinosis caused by a nonsense mutation, p.W138X (stop codon)[41,42], and five patients have recently undergone autologous HSPC transplantation.

Furthermore, new trials with cysteamine pro-drug and other drugs such as everolimus, which augments the effect of cysteamine, are the subject of extensive work in ongoing mRNA studies. The future of cystinosis treatment, therefore, seems bright.

Conflict of interest

None.

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