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REVIEW

Nephropathic cystinosis: an update on genetic conditioning

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Abstract

Cystinosis is an autosomal recessive lysosomal storage disorder caused by *CTNS* gene mutations. The *CTNS* gene encodes the protein cystinosin, which transports free cystine from lysosomes to cytoplasm. In cases of cystinosin deficiency, free cystine accumulates in lysosomes and forms toxic crystals that lead to tissue and organ damage. Since *CTNS* gene mutations were first described, many variations have been identified that vary according to geographic region, although the phenotype remains the same. Cystinosis is a hereditary disease that can be treated with the cystine-depleting agent cysteamine. Cysteamine slows organ deterioration, but cannot treat renal Fanconi syndrome or prevent eventual kidney failure; therefore, novel treatment modalities for cystinosis are of great interest to researchers. The present review aims to highlight the geographic differences in cystinosis—specifically in terms of its genetic aspects, clinical features, management, and long-term complications.

Keywords Cystinosis · Disparities · Geographic regions · Genetics · Clinical features · Management

Introduction

Cystinosis is an autosomal recessive disorder and the most common hereditary cause of renal Fanconi syndrome. The incidence of cystinosis is 1 in 100,000–200,000 live births [1]. Cystinosis is caused by *CTNS* gene mutations; the gene encodes the cystinosin protein that transports free cystine from lysosomes to cytoplasm. Cystinosin is an integral lysosomal membrane protein with 7 membrane domains [1, 2]. In cases of cystinosin deficiency, free cystine accumulates in lysosomes and forms cystine crystals that lead to tissue and organ damage [1, 2]. Multiple organs, particularly the kidneys, cornea, bone marrow, thyroid, muscle, peripheral nerves, liver, and spleen, are affected; however, kidney impairment is especially relevant to the prognosis.

The *CTNS* gene is located on chromosome 17p13.3 and consists of 12 exons, of which the first 2 are non-coding. Since the discovery of the C*TNS* gene in 1998, more than 140 mutations have been described [3, 4]; however, cystinosin deficiency and impaired cystine transport are the hallmarks of cystinosis. Cystinosin has additional roles, including regulation of autophagy, mTOR signaling, lysosomal biogenesis, and vesicle trafficking in proximal tubular epithelial cells [5].

There are 3 clinical forms of cystinosis based on the severity of kidney involvement and age of onset: infantile, juvenile, and ocular cystinosis. Infantile cystinosis known as infantile nephropathic cystinosis (OMIM #219800) is the most common (> 90% of patients) and most severe phenotype and is characterized by the development of renal Fanconi syndrome in infancy and kidney failure during the first decade if left untreated [1]. Juvenile cystinosis (sometimes referred to as late onset) accounts for approximately 5% of all cases. Onset of juvenile cystinosis is at age 10–12 years and is characterized by incomplete and mild renal Fanconi syndrome, along with prominent glomerular involvement and proteinuria. The non-nephropathic ocular form—ocular cystinosis—is limited to the eyes and presents with corneal cystine accumulation, rather than kidney disease.

With cysteamine treatment and kidney transplantation, the life expectancy of cystinosis patients can be prolonged and cystinosis managed as a multisystemic chronic disease; however, cysteamine treatment is insufficient for preventing kidney failure (chronic kidney disease stage 5 (CKD 5)) or treating renal Fanconi syndrome. As such, researchers endeavor to find more effective treatment strategies, such as hematopoietic stem and progenitor cell (HSPC) transplantation and novel drugs. The present review aims to highlight the geographic differences in cystinosis; specifically in terms of its genetic aspects, clinical features, management, and long-term complications.

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History and Epidemiology of Cystinosis

Since cystinosis was first described in 1903, knowledge of its pathogenesis, genetic basis, and treatment has vastly improved [3, 4, 6–8]. In European and US populations, the incidence is reported as 1 in 100,000–200,000 live births [5]; however, the incidence can be higher in selected populations, such as Brittany, France, and Quebec, Canada, due to founder mutations [5]. The frequency of the disease is also expected to be higher than expected in populations in which consanguineous marriage is widely practiced, including Turkey, the Middle East, Pakistan, and North Africa [9, 10].

Diagnosis

As cystinosis is the most common cause of renal Fanconi syndrome, its diagnosis is primarily based on the same standard clinical and biological criteria used to diagnose renal Fanconi syndrome, including failure to thrive, glucosuria, polyuria-polydipsia, electrolyte imbalance, dehydration, and/or rickets [1, 11]. Confirmation of the diagnosis is established based on the presence of corneal cystine crystals and/or a leukocyte cystine level > 2 nmol half-cystine mg^{-1} protein and/or identification of *CTNS* mutations [1, 11]. Diagnosis should be made as early as possible so as to ensure timely initiation of cysteamine treatment.

Clinical presentation, long-term complications, and some disparities

Patients with nephropathic cystinosis are normal at birth but then develop failure to thrive, growth retardation, polyuria, polydipsia, vomiting, dehydration, lack of appetite, constipation, rickets, and other symptoms of renal Fanconi syndrome by age 6 months, as well as the laboratory findings of renal Fanconi syndrome, including acidosis, glucosuria, aminoaciduria, hypophosphatemia, hypokalemia, and proteinuria. Although renal Fanconi syndrome is the first sign of kidney involvement, cystinosis affects glomerular podocytes and results in nephrotic-range glomerular proteinuria and focal segmental glomerulosclerosis [12, 13]. In time, kidney damage supervenes the clinical picture and leads to kidney failure at age 10–12 years if left untreated with cysteamine [1]. In patients that progress to CKD 5, kidney transplantation is the most appropriate treatment. The success rate of kidney transplantation and graft survival is good, and recurrence does not occur in the graft kidney [14].

The eyes are the second most commonly affected extra-renal organ, with cystine crystal deposits in the corneas. Cystine crystals can be observed in the cornea after age 1.5–2 years and are diagnostic of cystinosis (Fig. 1). Pigmentary retinopathy consisting of patches of depigmentation (Fig. 1) may sometimes be present as an early ocular finding and can result in impaired color vision and impaired night vision. Progressive retinopathy and band keratopathy occur later in life in patients not treated with cysteamine eye drops [11, 15].

The thyroid, pancreas, gonads, gastrointestinal system (GIS), muscles, bone marrow, bones, and central and peripheral nervous systems can be affected [1, 11, 15]. Almost all patients suffer from cystinosis metabolic bone disease related to renal Fanconi syndrome in infancy and CKD later in life. Manifestation of cystinosis metabolic bone disease is composed of hypophosphatemic rickets and renal osteodystrophy associated with CKD, which cause various skeletal deformities, such as O bein and X bein deformities, scoliosis, osteomalacia, fractures, short stature, and functional disabilities (Fig. 2). Furthermore, cysteamine toxicity in the presence of copper deficiency can cause bone disease [16, 17].

The most common endocrine complications are poor linear growth, pubertal delay, and hypothyroidism [18, 19]. Diabetes can occur as a late complication or in patients with poor control of the disease [18]. GIS findings include nausea, vomiting, feeding difficulty, anorexia, oral motor dysfunction, and dysphagia [20, 21]. Patients with good control of the disease have reduced rates of pubertal delay, hypothyroidism, and diabetes compared with patients with poor control of the disease [18]. Greco et al. [19] noted that patients treated at an early age had improved linear growth.

In terms of clinical presentation, there is not much difference between geographic regions, but, once again, it is expected that cystinosis will occur more frequently in parts of the world where the consanguineous marriage rate is high, such as in Turkey and Middle Eastern countries. Patients with fair hair are not as common in these regions as in the USA and Europe. Another difference between geographic regions could be due to obstacles in access to cysteamine treatment and cysteamine eye drops, especially in developing countries. Unfortunately, patients without access to cysteamine can be more prone to extra-renal involvement and early progress to kidney failure.

Genetic differences

In all, more than 140 *CTNS* mutations have been described in cystinosis patients worldwide. The most significant disparities are found in the genetic basis of the disease according to geographic region. The gene for cystinosis was first mapped to a 4-cM region of chromosome 17p13 in 1995 [3], and subsequently, this region was narrowed and the cystinosin gene *CTNS* was isolated by Town et al. [4] in 1998. A large 57-kb deletion involving the first 9 exons and part of exon 10 of the *CTNS* gene, along with 2 upstream genes *(CARKL and TRPV1)*, is the most common mutation that causes cystinosis in Northern

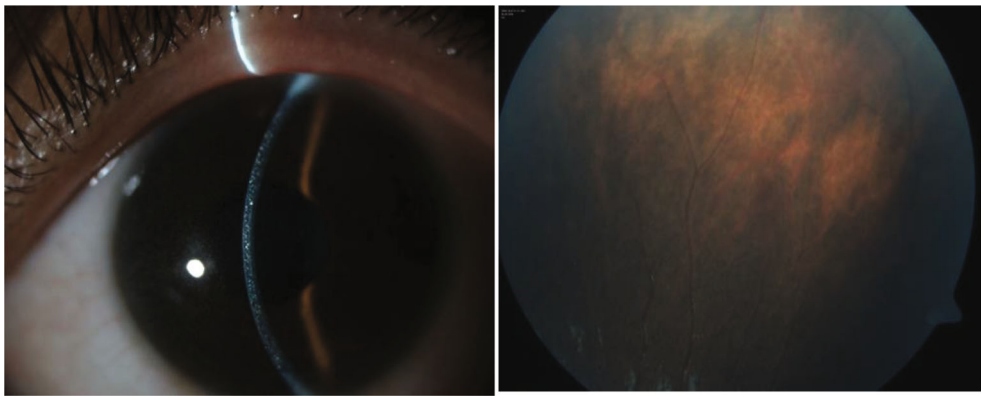

Fig. 1 Eye involvement

Europe and in North America [22, 23]. Germany is considered to be the country of origin for this 57-kb deletion. It first occurred in Germany around 500 AD and spread via migration throughout Europe [22]. In total, 44% of 108 patients in the USA with nephropathic cystinosis were homozygous for this deletion, followed by the c.753G-A (p.W138G) mutation [23]. In various parts of Northern Europe, it is reported to affect ~ 76% of alleles [24]. The frequency of this deletion is 22% in cases in Mexico [24]; however, it was shown that no patients in Turkey had the 57-kb deletion, indicating that its occurrence is reduced in the East Mediterranean and Middle East [10, 25]. Whereas the frequency of the 57-kb deletion is 50–70% in cases in Northern Europe and the USA, it is only 17% in Italy and 0% in Turkey [10, 25, 26]. However, a patient with this macro-deletion was recently reported in Iran, so while extremely rare, it is not completely absent in the Middle East [27].

A single-center Turkish study and a Turkish national study based on the national registry of cystinosis confirmed that the most common allele (31%) in Turkey is c.681G>A (p.E227E) [10, 25]. This mutation—a missense mutation that causes a frameshift—was first described by Aldahmesh et al. [28] in two Arab families. In Iran, the most common mutation is c.681G>A (p.E227E) [29]. Studies from Egypt show no cystinosis patients with the 57-kb deletion, but the c.681G>A (p.E227E) is common [30]. The high frequency of c.681G>A (p.E227E) in the Middle East indicates the existence of a possible founder mutation in this area.

c.1015G>A (G339R) is a founder mutation in the Ontario Amish Mennonite population in Canada. Although the Amish Mennonite population originated from Germany, they appear to only have the c.1015G>A (G339R) mutation, rather than the 57-kb deletion. This missense mutation was first described

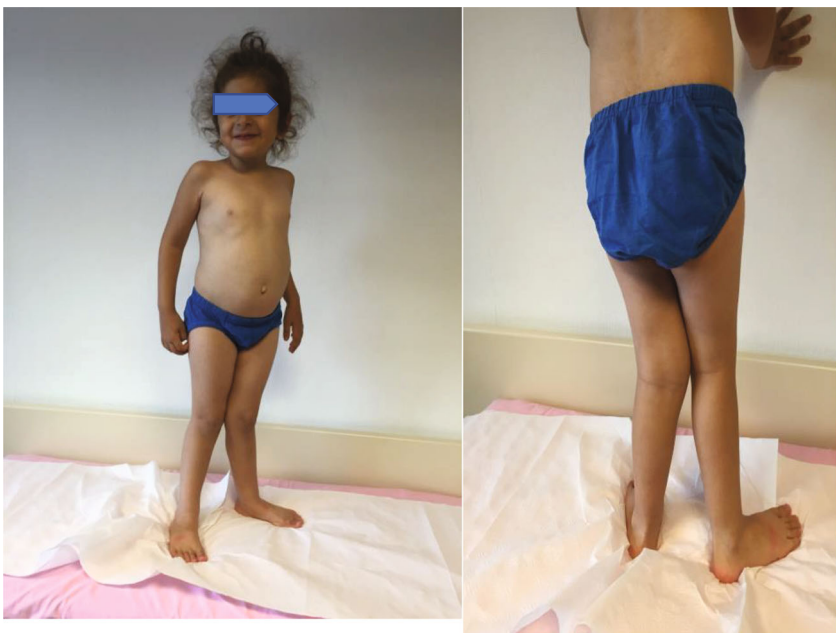

Fig. 2 X bein deformity

by Shotelersuk et al. [23] and is frequently observed in northern and southern Italy, Spain, Turkey, and the Middle East [10, 31]. Another founder mutation could be c.971-12G>A in the black population of South Africa [32].

A further mutation of interest is the nonsense stop codon mutation p.W138X, which accounts for 50% of cystinotic alleles in the French Canadian population, and was originally introduced from Ireland in the 1800s. This novel stop codon mutation shows the possibility for read through in the presence of an aminoglycoside, which may enable a potential treatment [33].

The impact of the various types of *CTNS* mutations has been investigated [23, 34, 35], and it is thought that individuals who harbor severe mutations, such as loss of function mutations on both alleles, have severe infantile cystinosis, whereas individuals homozygous or compound heterozygous for milder mutations have milder forms of cystinosis. Homozygosity for the 57-kb deletion was associated with an increased risk of morbidity and mortality [35]. A Turkish national study sought to better understand the effects of the mutations on clinical phenotypes and categorized mutations into 2 groups: missense mutations and severe mutations (deletions, duplications, and missense mutations that cause a frameshift). Although the duration of follow-up and mean cysteamine dosage were similar in both mutation groups, patients with missense mutations tended to have a better eGFR at the last follow-up visit than those with severe mutations (Fig. 3). However, the difference was not statistically significant, which might have been due to the fact that missense mutations have less of an effect on clinical prognosis [10, 25].

Treatment

It is crucial to control renal Fanconi syndrome with supportive treatment, so as to maintain normal fluid and electrolyte balance and prevent hypophosphatemic rickets and acidosis. Good control of renal Fanconi syndrome helps improve growth and quality of life. Moreover, indomethacin can be used to control polydipsia and polyuria associated with renal Fanconi syndrome after 6–9 months of age, but it should be used with great caution and withdrawn if dehydration, hypotension, or deterioration of kidney function occurs [16].

The specific treatment for cystinosis is cystine-depletion using cysteamine bitartrate in immediate-release or slow-release form [16, 36]. Early diagnosis and appropriate cystine-depleting treatment can significantly delay the progression to CKD 5 and prevent or delay extra-renal involvement [1, 37]. Another important issue related to cystinosis is the optimal time to initiate cysteamine treatment, which has the potential to ameliorate kidney complications. It is well known that mean age at CKD 5 among untreated patients is 9.6 years and that in treated patients functional kidney loss is postponed for 20 years [15, 19, 35]. Brodin-Sartorius [38] reported that the mean age at CKD 5 was 11.1 years and that patients who did not develop kidney failure started cysteamine treatment at a mean age of 1.5 years. According to a Turkish study [25], the mean age at CKD 5 was similar to that reported by Brodin-Sartorius [38] and that the time to kidney failure was longer in the patients in whom cysteamine treatment was initiated at age < 2 years (Fig. 4). In the context of the

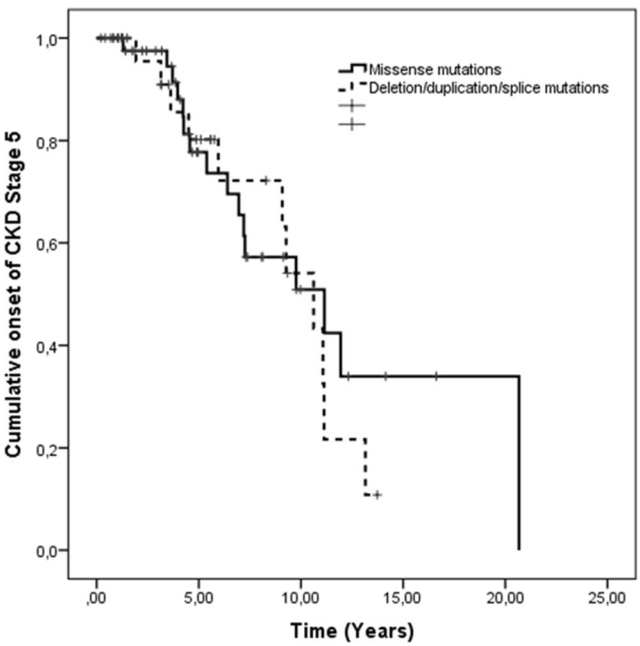

Fig. 3 Time to CKD 5 (years) of the patients with missense mutations (black line) vs. nonsense/frameshift/splice site mutations (grey line) (p = 0.79). (Composed using data from [10])

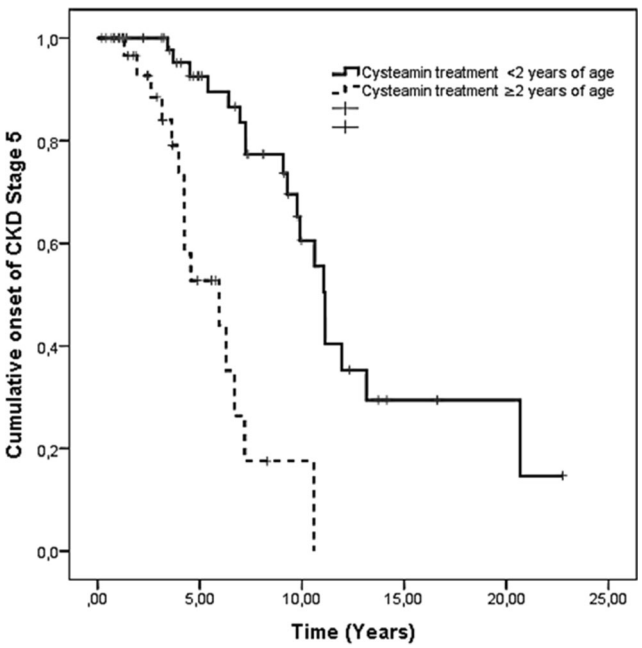

Fig. 4 Time to CKD 5 (years) of the patients with cysteamine treatment at age < 2 (black line) vs. ≥ 2 years old (grey line) p = 0.022. (Composed using data from [10])

treatment, the disparity resulting from the lack of adequate cysteamine treatment might be due to obstacles in access to treatment in developing countries, as well as poor treatment compliance.

The future of diagnosis and treatment

Measurement of LCL via liquid chromatography-tandem mass spectrometry (LC-MS/MS) is among the methods for diagnosing cystinosis and it is also used to monitor treatment; however, this method has several disadvantages, including that it is not practical or universally available and requires very sensitive storage and transport of samples.

Genetic testing is an excellent tool for diagnosis, as *CTNS* is a relatively small gene with only 10 coding exons, but is of no benefit to monitoring therapy. Some inflammatory markers and macrophage activation markers have been considered as potentially beneficial for monitoring cysteamine treatment. Chitotriosidase, which is produced by activated macrophages and several cytokines, including IL-1β, IL-6, and Il-18, is reported to be elevated in the plasma of cystinosis patients; however, these inflammatory factors are not specific to cystinosis [16]. Today's innovative technologies facilitate comprehensive screening of the entire genome, proteome, and metabolome. Detailed knowledge of genomic, proteomic, and metabolomic processes have converged in the integrated "omics" approach, which shows immense potential for increasing our understanding of the mechanisms of diseases that might result in early diagnostics, personalized therapeutic strategies, and improved assessment of treatment effectiveness.

The first allogeneic hematopoietic stem cell therapy (HSCT) for cystinosis was performed in 2018; although the patient initially showed some clinical improvement, the patient died due to multidrug-resistant sepsis [39]. Recently, two treatment modalities—autologous HSPC transplantation and a pharmacological treatment—have been described [33, 40]. Furthermore, human clinical trials and recruitment of patients aged > 18 years have been initiated for HSPC transplantation by Cherqui et al. [40]. A recent report demonstrated proof-of-principle for new pharmacological treatment of nephropathic cystinosis caused by a nonsense mutation, p.W138X (stop codon). The drug used, Geneticin G418, binds the ribosome and facilitates read through of the premature stop codon to produce functionally active protein in vitro, thus overcoming the nonsense mutation [33].

In conclusion, the literature indicates that the future for cystinosis is optimistic, as newer molecular and biochemical approaches and improved understanding of the disease are on the horizon.

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