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REVIEW

Nephropathic cystinosis: late complications of a multisystemic disease

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Abstract Cystinosis is a rare autosomal recessive disorder due to impaired transport of cystine out of cellular lysosomes. Its estimated incidence is 1 in 100,000 live births. End-stage renal disease (ESRD) is the most prominent feature of cystinosis and, along with dehydration and electrolyte imbalance due to renal tubular Fanconi syndrome, has accounted for the bulk of deaths from this disorder. Prior to renal transplantation and cystine-depleting therapy with cysteamine for children with nephropathic cystinosis, their lifespan was approximately 10 years. Now, cystinotic patients have survived through their fifth decade, but the unremitting accumulation of cystine has created significant non-renal morbidity and mortality. In this article we review the classic presentation of nephropathic cystinosis and the natural history, diagnosis, and treatment of the disorder's systemic involvement. We also emphasize the role of oral cysteamine therapy in preventing the late complications of cystinosis.

Keywords Cystinosis · Nephropathic · Complications · Lysosomal storage · Transport

Introduction

The classical, infantile, form of nephropathic cystinosis, first described in the early twentieth century by Aberhalden, proceeds inexorably to renal failure [1, 2]. Less severe presentations, however, can occur. Late onset (juvenile or intermediate) cystinosis manifests renal disease, but with onset of symptoms in adolescence. An ocular, non-nephropathic, form of cystinosis, previously termed adult or "benign" cystinosis, presents with photophobia, rather than renal disease, and crystals form in the cornea and bone marrow [1].

Early symptoms of classical nephropathic cystinosis include renal tubular Fanconi syndrome, rickets, impaired growth, hypothyroidism, and photophobia [3]; cystine crystals are apparent on slit lamp examination of the cornea from 16 months of age [4]. Infantile nephropathic cystinosis has a range of severity, but end-stage renal disease (ESRD) invariably occurs at approximately 10 years of age [5]. In the late 1960s, renal transplantation came into increasing use, and the lifespan of cystinotic patients was markedly prolonged. However, cystine accumulation continued in non-renal organs, including the muscle, brain, bone marrow, liver, spleen, lymph nodes, cornea, conjunctiva, thyroid, pancreas, testes, and intestines [1, 6]. Consequently, the clinical course of cystinosis changed from that of a largely renal disease to that of a multisystemic disorder with significant non-renal involvement, including a distal vacuolar myopathy, decreased pulmonary function, swallowing impairment, deterioration of the central nervous system (CNS), endocrinopathies, vascular calcifications, retinal damage, and other ophthalmic complications [2, 7].

At the same time, the treatment of cystinosis changed entirely from treatment of the symptoms to a therapy directed toward the basic defect, i.e. lysosomal cystine accumulation. In fact, diligent treatment with the cystine-depleting free thiol cysteamine was found to delay renal deterioration, enhance growth, and prevent several of the late, non-renal complications of cystinosis [8–16]. The availability of renal transplantation and cysteamine therapy

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has transformed a lethal pediatric disease into a treatable chronic disorder.

Other reviews address cystinosis primarily as a pediatric disease [3] or as a genetic disorder [1]. This review emphasizes the late, non-renal, manifestations of nephropathic cystinosis and the effects of cystine-depleting therapy on these complications. As background, we first provide fundamental information about cystinosis and its presentation early in life.

Genetics and basic defect

The cystinosis gene, *CTNS*, resides on chromosome 17p13 [17]. *CTNS* has 12 exons and encodes an integral lysosomal membrane protein called cystinosin, which contains 367 amino acids and functions as a cystine carrier [18, 19]. The most common *CTNS* mutation, a 57-kb deletion, arose in Germany approximately 1,500 years ago and affects nearly half of all North American and European patients [20]. An isolate of cystinotic patients bearing a W138X mutation exists among French Canadians [21]. More than 50 additional genetic mutations have been described [20–24]. Patients with classical cystinosis have deletions or other mutations associated with the loss of a functional protein, whereas milder cases (with intermediate or ocular cystinosis) are heterozygous for a severe (e.g. nonsense) mutation and a milder (e.g. splice-site) mutation [22, 25].

Normally, cystinosin transports cystine out of intracellular lysosomes and into the cytoplasm in a saturable and ligand-specific fashion [26, 27]. Heterozygotes for cystinosis, who never manifest clinical symptoms, exhibit half the normal cystine-transporting capacity [28], and this is sufficient to maintain cellular cystine levels close to the normal range [1]. In general, the severity of clinical illness correlates directly with the amount of cystine storage and inversely with the amount of residual transport capacity [29, 30]. Other factors, such as modifying genes or environmental influences, may also operate in certain individuals to influence the phenotype.

One clear sign of impaired lysosomal cystine transport is crystal formation, which occurs as a result of the poor aqueous solubility of cystine (~1 mM). The crystals are generally hexagonal or rectangular, but can also be needle-like (Fig. 1); they are birefringent under polarized light. The extent of crystal formation does not correlate with the severity of damage to a tissue. For example, the liver and intestine have immense intracellular cystine crystal formation, and yet they manifest symptoms only rarely. This may be explained by the extensive functional reserve of certain organs, or by their rapid rates of cell turnover. Cultured cells such as fibroblasts or lymphoblasts have elevated cystine content but do not contain crystals [1].

We do not know how cystine accumulation leads to the pathology of nephropathic cystinosis. One hypothesis, that lysosomal cystine causes increased cellular apoptosis [31], derives from the fact that lysosomes participate in the

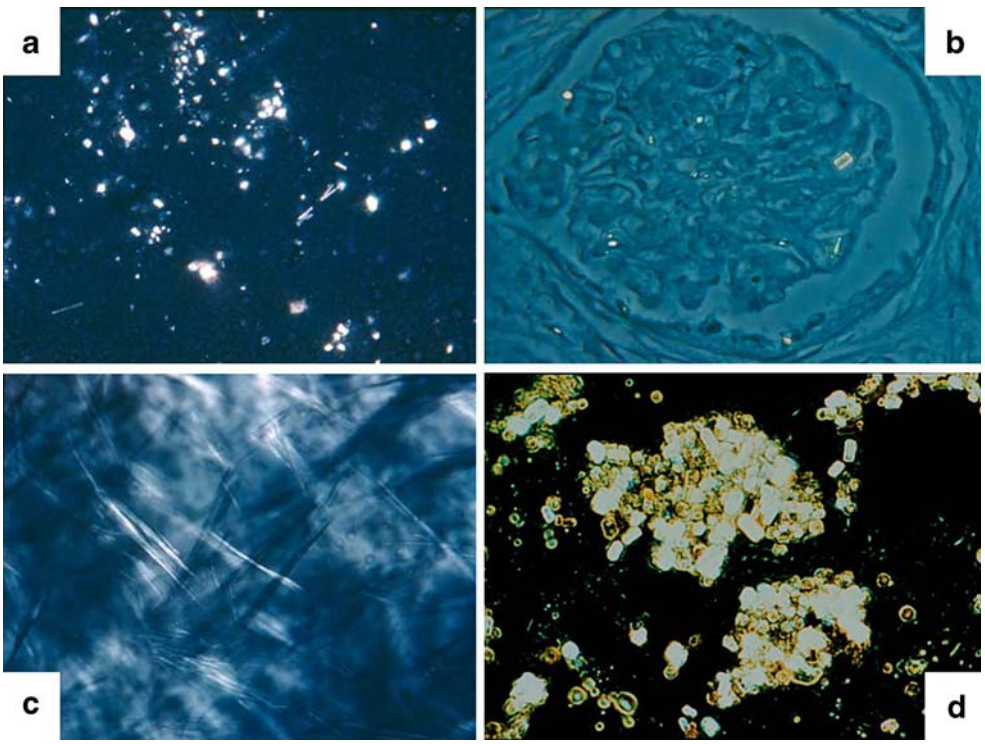

Fig. 1 Cystine crystals in tissues of nephropathic cystinotic patients. **a** Liver; **b** kidney; **c** cornea; **d** bone marrow

important process of programmed cell death [32]. Apoptosis causes some forms of retinopathy, and it could explain the early renal tubular dysfunction and other aspects of the cystinosis phenotype. Alternatively, complications such as renal Fanconi syndrome could represent secondary metabolic phenomena [24]; the Fanconi syndrome appears without substantial cystine crystal deposition in the renal tubules and does not improve significantly with cystine-depleting therapy. Nevertheless, immortalized human proximal tubular cells express the lysosomal cystine transport defect [33].

Animal models could help elucidate the pathogenesis of some features of cystinosis. Cherqui et al. reported the clinical, histological and biochemical phenotype of the *Ctns-/-* mouse [34]. In this model, the cystinosin protein is truncated, mislocalized and nonfunctional. The *Ctns-/-* mice accumulate cystine in all organs, and typical cystine crystals are formed in several tissues. The null mice also manifest characteristic ocular changes, bone defects and behavioral abnormalities but do not develop features of proximal tubulopathy or renal failure, despite their high renal cystine content [34].

Cystinosis pre-transplantation

Clinical characteristics

The various signs and symptoms of cystinosis occur at different ages (Table 1). The condition of patients is normal at birth, and they typically present with poor growth at 6–12 months of age; they develop rickets at approximately 1 year of age, photophobia in early childhood, and renal glomerular failure before adolescence [3, 8].

Renal involvement The renal manifestations of cystinosis involve overlapping pathologies [35]. The major effects of nephropathic cystinosis include the onset of renal Fanconi syndrome prior to 1 year of age, followed by progressive loss of glomerular function culminating in renal failure at 7–12 years of age [3].

The renal pathophysiology of cystinosis has not been elucidated [36, 37], but the disorder is recognized as the most common identifiable cause of renal Fanconi syndrome in childhood. Patients exhibit fluid and electrolyte losses, aminoaciduria, glucosuria, phosphaturia, hypercalciuria, and hypochloremic acidosis. Urine volume can be so great that some patients are diagnosed with nephrogenic diabetes insipidus and pseudohypoaldosteronism [1]; only later is the true Fanconi syndrome recognized. In some children the large losses of calcium and phosphate result in medullary nephrocalcinosis [38]. Hypophosphatemic rickets, with a high fractional excretion of phosphate, normal vitamin D levels, and elevated levels of serum alkaline phosphatase, is characterized by osteomalacia, bone deformities and delayed ambulation [3, 39] The hypercalciuric hypocalcemia of cystinosis can cause tetany. Hypokalemia, sometimes with potassium levels below 2.0 mEq/l, can threaten cardiac conduction. Carnitine is also lost in Fanconi syndrome [40], and this may lead to poor muscle development [41]. Fanconi syndrome also causes tubular proteinuria, with urinary losses of low molecular weight proteins such as retinol binding protein, albumin, and beta-2-microglobulin. Some pre-dialysis patients have had urinary protein levels in the nephrotic range [42, 43].

Cystinosis accounts for approximately 5% of chronic renal failure in children [44]. The European Dialysis and Transplant Association Registry found that the median age of children starting renal replacement therapy for cystinosis was 9.5 years, with a range of 1–20 years [5]. The rate of development of ESRD differs among cystinotic patients; some reach a plateau in their renal function, while the condition of others deteriorates rapidly [2, 45]. Infants as young as 18 months have been known to suffer from renal insufficiency [46], but their serum creatinine seldom exceeds 1 mg/dl before they reach 5 years of age.

The histopathology of Fanconi syndrome in cystinosis involves “swan neck” deformities and cellular atrophy of the proximal renal tubules [47]. Cystine crystals have been detected in the epithelial cells and epithelial lamina of the kidney in cystinotic patients [48]. Cystinotic glomeruli show focal and segmental glomerulosclerosis [1]. There is a possibility that tubular dysfunction decreases glomerular filtration rate (GFR) due to activation of a glomerular–tubular feedback mechanism [5].

Growth retardation and endocrine involvement Various degrees of renal damage, acidosis, metabolic bone disease,

Table 1 Clinical findings in children with nephropathic cystinosis

Age	Presentation
Birth	Normal
Infancy	Renal tubular Fanconi syndrome
	-Dehydration, polyuria, polydipsia
	-Metabolic acidosis
	-Hypokalemia
	-Hypophosphatemic rickets
	-Hypocalcemic tetany
	Growth retardation
	Vomiting
Early Childhood	Photophobia
Pre-adolescence	Renal failure
	Renal osteodystrophy
	Hypothyroidism

hypophosphatemic rickets, nutrient losses, and hypothyroidism [49, 50] contribute to profound growth retardation in children with cystinosis. It has also been proposed that poor bone maturation in cystinosis could be related to deficiency of renal 1-alpha hydroxylase [51]. The bone age of cystinotic children is retarded compared with chronological age [1, 2, 3]. In the natural history of cystinosis, infants are at the third percentile for height by 1 year of age, and they grow at a much slower rate than healthy children, i.e. at ~50–60% of normal [11]. This growth is worse than for children with end-stage renal disease due to other causes [52]. Treatment with growth hormone dramatically increases linear growth and significantly improves height velocity and statural height in prepubertal cystinotic patients [53].

Compensated hypothyroidism, leading to frankly low thyroxine levels, occurs frequently in cystinosis and may contribute to growth retardation. Histological examination of the thyroid glands reveals extensive destruction and infiltration of the epithelium with cystine crystals [54]. Postmortem findings include follicular atrophy of the thyroid glands, with hyperfunctioning thyrotrophs in the pituitary gland [55]. Patients with cystinosis appear to have pituitary resistance to thyroid hormone, and the increase in serum thyroid-stimulating hormone (TSH) is often associated with high levels of TSH-alpha [50]. These abnormalities return to normal following low-dose thyroxine treatment [56].

Ocular manifestations Early ocular manifestations of cystinosis include crystals in the cornea and conjunctiva. Corneal crystals usually appear as needle-shaped, reflectile, opacities (Fig. 1c), visible on slit-lamp examination [4]. Photophobia occurs in the first or second decades and varies extensively in severity. Although cystine crystals themselves rarely affect visual acuity, they create a hazy cornea and sometimes lead to a band keratopathy (Fig. 2a), which can impair vision. Crystals are also sometimes deposited in the anterior chamber, iris, ciliary body, choroid, fundus and optic nerve [15, 57]. A pigmentary retinopathy, sometimes apparent earlier than corneal crystals [58], consists of patches of depigmentation [59]. Focal destruction of photoreceptors has also been reported [60], and fluorescein angiography reveals areas of devascularization.

Other findings Cystinosis also affects other glandular functions. Sweating [61], salivation, and tear production are reduced, even in childhood, and patients suffer from heat avoidance, hyperthermia, flushing, vomiting and dry eyes [3]. Lubrication with ordinary saline drops relieves the eye discomfort [8]. The formation of crystalline cystine deposits in the gingiva has been described on electron microscopy [62]. Patients often suffer anemia, associated with cystine crystals in the bone marrow [63], decreased renal production of erythropoietin, or uremia. Hypocoagulability, as well as platelet dysfunction, have also been reported in cystinotic patients [64].

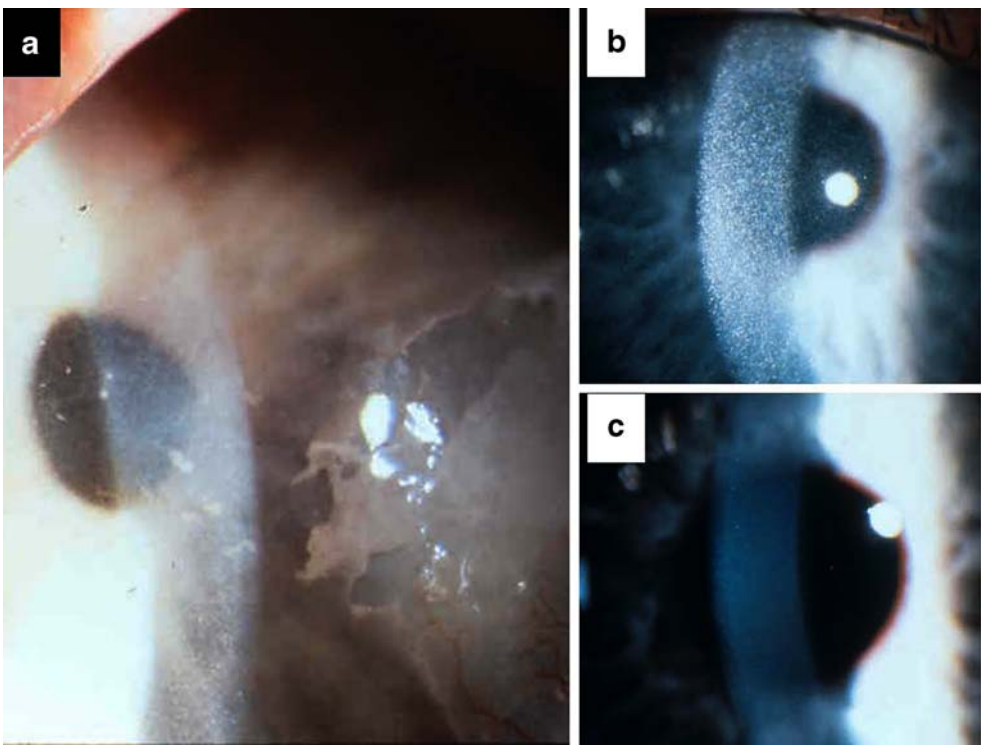

Fig. 2 Findings of slit lamp examination of the eye in patients with cystinosis. **a** Band keratopathy in a 33-year-old patient. There is a paucity of crystals after cysteamine eyedrop therapy, which does not dissolve the calcified band. **b** The untreated cornea of a 43-month-old patient. **c** The same child 12 months later, after consistent cysteamine eyedrop therapy

Diagnosis and laboratory evaluation

Early diagnosis is crucial for cystinotic patients, in order that preventive and therapeutic management, including cystine-depleting therapy [65] be started. The symptoms of nephropathic cystinosis have a broad differential diagnosis, but a family history combined with certain clinical and laboratory findings, particularly those associated with renal tubular Fanconi syndrome, may be highly suggestive. In addition to growth retardation, polyuria and polydipsia also affect infants, who often urinate 2–6 l per day [3]. Aminoaciduria and increased secretion of solutes, particularly phosphate, should prompt investigations into cystinosis. Chemical analyses of serum reveal hypokalemia, acidosis, elevated levels of alkaline phosphatase, and, sometimes, hypocalcemia and hypercholesterolemia. Urine electrolyte excretion is increased, urine specific gravity is very low, and tubular proteinuria is evident [3]. Elevated TSH and reduced free thyroxine levels can be seen in mid–late childhood.

The diagnosis of cystinosis is confirmed by measurement of the cystine levels in mixed leucocyte preparations moderately enriched in polymorphonuclear leucocytes or, previously, in cultured fibroblasts [1]. Cystine concentrations in individuals with classical nephropathic cystinosis are 5–23 nmol half-cystine/mg cell protein; in heterozygous individuals, the levels are less than 1.0 nmol half-cystine/mg cell protein (normal <0.2 half-cystine/mg cell protein). Leucocyte cystine values in ocular cystinosis are generally 1–3 nmol half-cystine/mg protein, and, in intermediate cystinosis, they are slightly higher [1]. Corneal crystals are apparent on slit lamp examination after 16 months of age [4]. Their appearance can be confirmatory for the diagnosis of cystinosis, but the absence of corneal crystals should not be used to exclude the diagnosis, especially in infants. A variety of tissues, including bone marrow, conjunctiva, and kidney, have been biopsied to diagnose cystinosis [1], but these invasive procedures are no longer indicated.

When a previous sibling has been diagnosed with cystinosis, prenatal diagnosis can be made by measurement of elevated free cystine levels in cultured amniocytes or samples of chorionic villi [1]. Neonatal diagnosis can be achieved by the measurement of cystine in the placenta or in leucocytes after birth, prompting rapid initiation of treatment [1].

Treatment

Treatment of cystinosis can be divided into the management of symptoms and complications, and specific therapy targeting the root cause of the abnormality, i.e. lysosomal cystine accumulation.

Treatment of symptoms

Prior to renal transplantation, replacement of renal losses due to Fanconi syndrome is life-saving. This includes provision of fluids and electrolytes, especially potassium, citrate, bicarbonate therapy or Scholl's solution, and phosphate (for hypophosphatemic rickets). Vitamin D is often used to enhance gastrointestinal phosphate absorption, and calcium may be needed to prevent and treat tetany. Thyroxine replacement is commonly required. Children whose height remains below that of the third percentile can benefit from growth hormone therapy. An example of the specific treatment of an infant with cystinosis has been published [3].

For ESRD, hemodialysis and peritoneal dialysis are temporizing measures while patients await renal replacement therapy. When a live donor is available, pre-emptive transplantation is preferred. Both living donor kidneys and cadaveric kidneys perform very well in cystinotic patients. Advances in anti-rejection medications have vastly increased the pool of potential kidney donors for cystinotic patients, and heterozygous relatives are included among the acceptable donors. Recently, the use of steroid-free immune suppression has been employed in selected centers. Retention of the native kidneys can result in persistence of renal tubular Fanconi syndrome in cystinotic patients that have received transplants, but the donor kidney does not itself develop Fanconi syndrome. Cystine crystals can be observed in a donor kidney, but this occurs because of invasion of host cells; the crystals appear in the interstitium and not in the tubular epithelium. Renal transplantation does not correct the systemic metabolic defect of cystinosis.

Cystine-depleting therapy: cysteamine

In 1974, Thoene et al., reasoning that storage of cystine causes the manifestations of the disease, began to study agents that could potentially deplete cystine [66]. They found that an aminothiol, cysteamine (Beta-mercaptoethylamine), rapidly depletes cystinotic fibroblasts of cystine. Later, they demonstrated the mechanism of cystine depletion by cysteamine [67]. The free thiol traverses the plasma and lysosomal membranes to participate in a disulfide interchange reaction with cystine inside the lysosome. The two products formed, cysteine and cysteine–cysteamine mixed disulfide, both exit the cystinotic lysosome by a process not requiring the mutant cystinosin protein [68]. In fact, the mixed disulfide leaves via a lysine transporter [67].

Cysteamine, administered orally at the dose of 60 mg/kg per day to 90 mg/kg per day [69] every 6 h, can deplete intracellular cystine by 90% [1, 70]. Leucocyte cystine measurements are used to gauge compliance and adequacy of dosing [69]. In the 1980s and 1990s, long-term oral

administration of cysteamine was shown to retard the rate of renal glomerular deterioration and to improve linear growth of children with cystinosis [11, 71]. Later, retrospective analysis of 30 years of experience at the National Institutes of Health demonstrated much improved creatinine clearance and growth in cysteamine-treated compared with those in untreated patients [12]. In fact, early cysteamine therapy actually allowed for growth of renal capacity, rather than loss of glomerular function, in the first 3 years of life. Other data address the effectiveness of cysteamine in preventing damage to different parenchymal organs [72], including the thyroid [13]. Oral cysteamine therapy is now the treatment of choice for pre-transplant cystinotic patients [73] and was approved by the United States Food and Drug Administration in 1994 as Cystagon [1].

Cysteamine, however, has its drawbacks. It tastes and smells foul, and 10–15% of patients do not tolerate a full dosing regimen [74]. Many patients suffer nausea, vomiting and gastrointestinal discomfort, perhaps due to stimulation of gastric acid and gastrin production [75]; proton pump inhibitors may be helpful in this regard. Responses to cysteamine treatment are variable, reflecting genetic heterogeneity. The Fanconi syndrome of cystinosis does not appear to respond to long-term cysteamine therapy. Finally, with respect to renal glomerular function, an optimal response requires early treatment [16, 47, 76, 77].

While orally administered cysteamine exerts striking systemic effects in cystinosis, it does not dissolve corneal cystine crystals. For that, topical cysteamine eyedrops (0.55%, given 6 to 12 times per day) are required. This treatment can dramatically ameliorate the photophobia of cystinosis within weeks, decreasing the risk of blepharospasm. The drops can dissolve corneal cystine crystals completely within 1 or 2 years, often clarifying the cornea (Fig. 2b, c) [4, 78, 79]. Corneal transplantation [80] is seldom indicated for the corneal crystals of cystinosis.

Cystinosis after transplantation

The availability of renal transplantation for patients with nephropathic cystinosis has created the first generation of adults with this disease [81, 82], revealing the complications of long-standing intracellular cystine accumulation and, recently, the efficacy of long-term oral cysteamine therapy.

Late disease complications

The involvement of different organ systems in post-transplant individuals with cystinosis means that, without long-term cysteamine therapy, almost every patient will have suffered some major complication by the time they reach 30 years of age [7, 83]. In many cases, a single organ is much more seriously involved than another. Patients with relatively mild renal disease, for example, can manifest the most severe myopathy. Despite the serious medical issues that patients experience, many treated adults function well in their personal and professional lives.

Growth retardation The growth of adults with cystinosis who have not received significant cystine-depleting therapy is severely retarded (Fig. 3a). Adult heights average 144 cm, or approximately 25 cm below the normal mean. Adult weights approximate 45 kg, or 25 kg below normal [1, 83].

Progressive myopathy with muscle wasting Skeletal and pharyngeal muscle involvement occurs commonly in cystinotic patients who survive into their twenties and thirties without cysteamine therapy. The myopathy presents with atrophy and progressive distal weakness, first involving the thenar and hypothenar eminences and the interosseous muscles of the hands, which assume a claw-like posture (Fig. 3b). Later, dysphagia and generalized atrophy supervene [84, 85]. The absence of any sensory deficit correlates with symptoms typical of spinal muscular atrophy. Electromyography shows a myopathic pattern; nerve conduction velocity is normal [84–86]. Muscle biopsy demonstrates prominent unrimmed vacuoles with small ring fibers but no evidence of endomysial inflammation. Electron microscopy shows the typical rectangular appearance of cystine crystals within perimysial collagen fibrils (Fig. 3c) [85]. Free cystine levels in cystinosis muscle increase with age up to 1,000 times greater than normal [72]; even cystinosis myotubes in culture store excess cystine [87]. The increased cystine content of muscle is considered the cause of the vacuolated myopathy of cystinosis [85]. Plasma and muscle carnitine deficiency, impairing mitochondrial fatty acid metabolism, can contribute to lack of energy in muscles, but that occurs early in life because of the Fanconi syndrome; it is not likely to be the cause of the late myopathic complications.

Significant muscle wasting leads to progressive oromotor dysfunction, including dysphagia [88, 89]. Trauner's group described different types of oromotor dysfunction, such as communication and feeding problems, a hyperactive gag reflex, inability to elevate the palate, hoarse voice, inability to perform normal jaw movements, and absent gag reflex [89]. Almost half of the individuals studied showed evidence of at least mild muscle weakness in addition to gross and fine motor impairment on neurologic examination. Sensory and motor nerve conduction velocities and action potentials were in the normal range on electromyography [86].

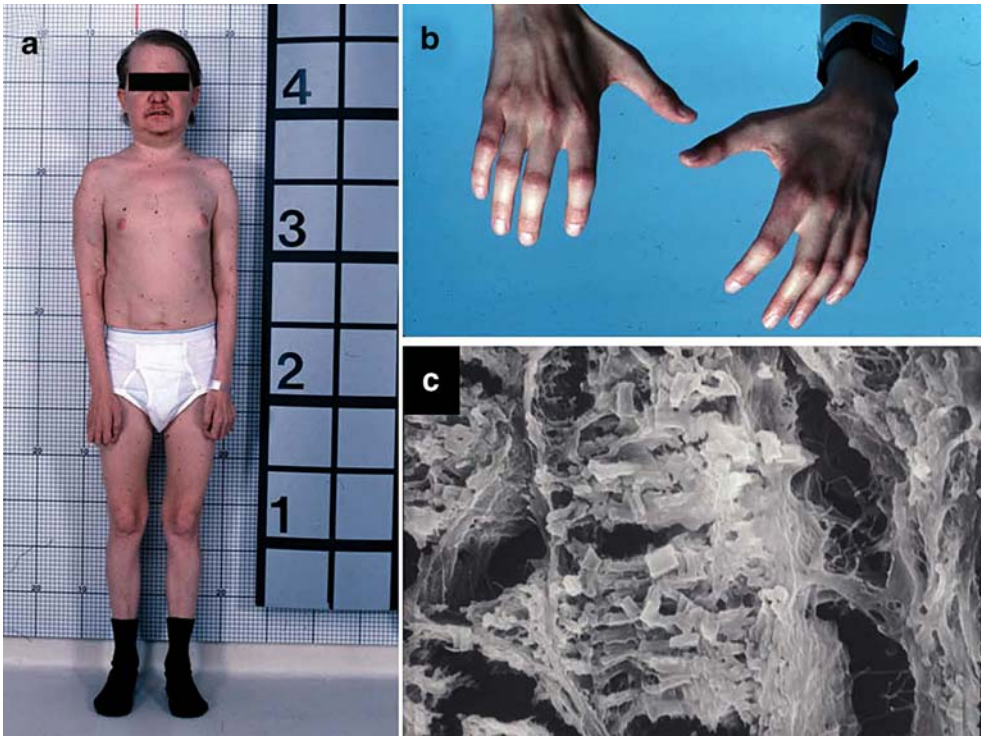

Fig. 3 Muscle involvement in cystinotic patients who did not receive oral cysteamine therapy. **a** Short stature, atrophic musculature, claw hands, and squinting in a 30-year-old man with cystinosis. **b** Flexed position of hand and atrophy of interosseous muscles in a 23-year-old man with nephropathic cystinosis. **c** Cystine crystals in the hand muscle of a 19-year-old woman with cystinosis

Progressive myopathic findings also appear in accessory chest muscles, causing extraparenchymal restriction of ventilation. Pulmonary function test results consist of reduced values for maximal inspiratory pressure, maximal expiratory pressure, and maximum voluntary ventilation, indicating decreased respiratory muscle strength and endurance [90]. Pulmonary insufficiency caused by general thoracic muscle weakness is a severely debilitating and sometimes life-threatening complication of cystinosis.

The swallowing difficulties in cystinosis, which progress slowly but inexorably, are attributed to destruction of pharyngeal muscles as part of the generalized vacuolar myopathy [88]. Accumulation of cystine in muscle cells causes deterioration of oropharyngeal muscles, which correlates with muscular dysfunction. Sonies et al. evaluated swallowing phases with videofluoroscopy, using a modified barium swallow study and employing a swallowing severity score to reflect the degree of dysfunction [88]. The scores ranged from normal bolus flow and duration (score of 1) to severe dysphagia with aspiration (score of 4). The majority of patients had significant symptoms of swallowing difficulties such as slow eating (49%), xerostomia, heartburn, choking and airway obstruction (20%), and pain with swallowing (7%). Many patients manifested hypophonic speech and had poor tongue and lip strength. Nine patients had recurrent episodes of aspiration that may have prompted their deaths [14, 88]. Because swallowing difficulties can lead to aspiration pneumonias, feeding problems and poor nutrition, some patients should be examined for placement of a feeding tube.

Central nervous system involvement Although rare, CNS complications do occur in adults with cystinosis. Most commonly, a generalized cerebral atrophy is apparent on brain CT scan, occasionally with superimposed calcifications of the basal ganglia and periventricular areas (Fig. 4a). A cystinosis encephalopathy involves mental deterioration, impaired cerebellar function, and pyramidal signs. Its occurrence does not correlate with other extrarenal complications of cystinosis, but its frequency does correlate directly with age [91]. The pathogenesis could be related to neurotoxicity involving oligodendrocytes. Another constellation of clinical symptoms includes progressive bradykinesia, dementia and spasticity [92]. In some patients with profound neurological deficits, CT scans revealed cerebral involvement with atrophy, multifocal cystic necrosis, dystrophic calcification, extensive demyelination of the internal capsule, spongy changes in the brachium pontis, and vacuolization [93, 94]. Electron microscopy showed deposition of cystine crystals in membrane-bound cytoplasmic vacuoles of pericytes and within parenchymal cells of white matter [95].

Another aspect of cerebral involvement in cystinosis is idiopathic intracranial hypertension, or pseudotumor cerebri, presenting as headache, papilledema and ophthalmoplegia [96]. Examination of the cerebrospinal fluid (CSF) gives normal findings, except for elevated pressure. Hypercoagulability due to renal disease, or impaired CSF resorption in the arachnoid villi due to cystine deposition, might lead to the development of idiopathic intracranial hypertension in cystinosis. In most cases, acetazolamide

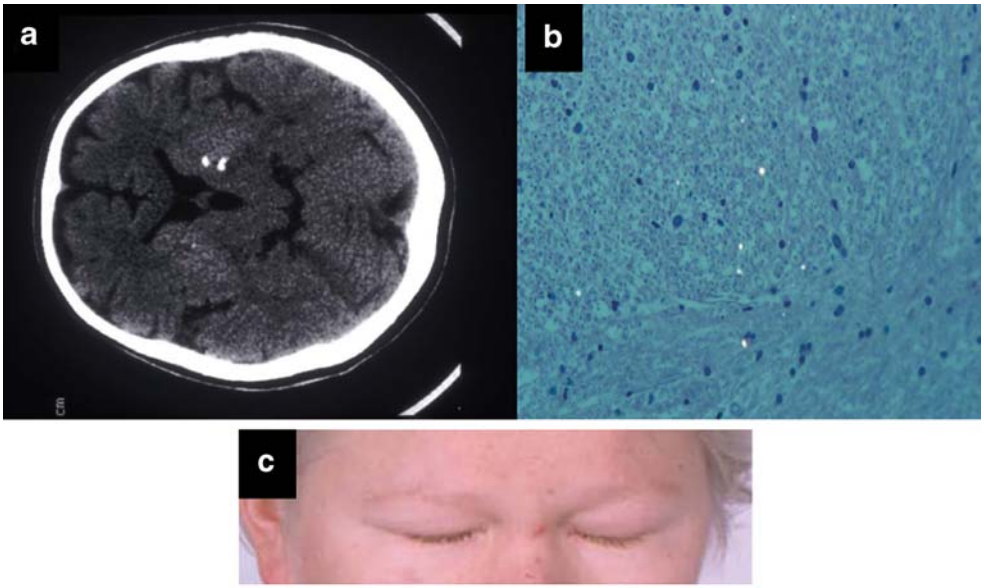

Fig. 4 Late complications of nephropathic cystinosis not well treated with oral cysteamine therapy. **a** CT scan of the head of a 36-year-old woman, showing cerebral calcifications. **b** Light microscopic slide of the testis of a 22-year-old man, showing fibrosis and scattered cystine crystals. **c** Blepharospasm in a 20-year-old man

treatment or ventriculoperitoneal shunt placement resolves the condition.

Non-absorptive hydrocephalus [97], convulsions, spasticity, cerebral atrophy, ischemic lesions, and multifocal mineralization have also been reported in cystinosis. Some cystinotic patients have abnormal encephalogram results, without seizures [98].

Some later neurological characteristics of cystinotic patients reflect findings that presented earlier in life. Children with cystinosis have mean full scale IQs in the low normal range [99–101], with impaired tactile recognition of common objects and difficulty processing visual information [102, 103]. Even children with normal composite IQs have low visual memory subtest scores, and their academic performance is usually lower than normal. Only one study has evaluated the relationship between brain structural changes and cognitive performances. Nichols et al. showed an association between the degree of cortical atrophy and the severity of impairment in visual short-term memory performance [104]. Others reported that children with cystinosis are at greater than normal risk for developing behavioral difficulties and social problems [99, 105]. Besides cystinosis, renal failure, long-standing dialysis, and growth retardation themselves can lead to difficulties in psychosocial adjustment requiring psychotherapy.

Ctns-/- mice with cystinosis exhibit behavioral abnormalities consisting of decreased activity and a tendency to walk along the walls of their cages [34].

Cardiovascular Arterial hypertension is well-documented in patients with nephropathic cystinosis and ESRD, the majority of whom have renin-dependent hypertension [56]. Blood pressure usually returns to normal after removal of the native kidney. Calcification of various vessels, primarily the coronary arteries, is one of the late complications of cystinosis in patients with transplants [106]. High-resolution CT scans have revealed calcifications in the internal carotid arteries, coronary arteries, aortic arch and abdominal aorta. Most patients with vascular calcifications had not received significant cysteamine therapy, which is consistent with the conclusion that cystinosis itself, and not drug exposure, is a risk factor for this complication. Adult patients should be carefully monitored for myocardial ischemia; some may require stenting or bypass surgery [106]. The hypercholesterolemia of cystinosis [107] also puts patients at increased risk of developing cardiovascular complications.

Cardiomyopathy and death associated with a ruptured pseudoaneurysm has been documented in one patient [108]. Four patients have been described with coronary artery dilatation, and one with an aneurysm in the descending aorta [109, 110]. There are reports of myocardial cystine deposition, and electron microscopy has revealed rectangular intralysosomal crystals within interstitial histiocytes adjacent to myocytes [108].

Endocrine involvement In patients with nephropathic cystinosis, growth improves after restoration of renal function by kidney transplantation [111]. Hypothyroidism, however, becomes more frequent in post-transplant patients without cysteamine therapy, so that three-fourths of cystinotic patients require thyroid hormone supplementation by the time they are 30 years old [8, 13]. In addition, untreated cystinotic patients nearly always exhibit late sexual maturation. In male patients, puberty starts at 16–17 years of age, and many show evidence of primary hypogonadism [112]. Parenchymal tissue destruction and cystine accumulation within the testes have been reported in late stages of the

disease (Fig. 4b) [113]. Winkler et al. suggested that male patients develop hypergonadotropic hypogonadism due to progressive alteration in the gonadal tissue [111]. In fact, most untreated men with cystinosis have low levels of testosterone and high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and may benefit from testosterone supplements to restore secondary sexual characteristics. Infertility appears to be common in men [112]; no cystinotic patient is known to have fathered a child, although the ability to have an erection apparently remains intact. Girls generally reach puberty at 14–15 years of age [8]. Ovulatory cycles and gonadal endocrine parameters appear normal in female patients [111], and successful pregnancies and deliveries have been observed in women with cystinosis [114]; the condition of the offspring has been completely normal.

Although hypothyroidism was initially considered to be the only endocrinopathy of cystinosis, the development of diabetes mellitus in post-transplant patients has been repeatedly documented [55, 115–117]. Hyperglycemia is exacerbated by the use of prednisone after transplantation, and its frequency has been reported at 50–80% of young adults with cystinosis [55]. Postmortem results have shown a markedly increased pancreatic beta cell fraction [1], possibly due to cystine's interference with insulin secretion. The findings of oral glucose tolerance tests are abnormal [55, 118], and many patients require insulin replacement therapy.

Gastrointestinal complications Untreated cystinotic patients can develop gastrointestinal symptoms in the second or third decade of life. The spectrum of involvement is diverse, and the frequency is greater than previously recognized. In patients of all ages, approximately 77% have documented feeding abnormalities due to reflux, dysmotility, pseudo-obstruction, or swallowing dysfunction [119].

Mild hepatomegaly, a common feature of nephropathic cystinosis [1], is rarely associated with overt symptoms of liver cell dysfunction. One case of hepatic veno-occlusive disease has been reported [120]. Two cases of portal hypertension have been described, with evidence of nodular regenerative hyperplasia [121], but the pathogenesis remains to be defined. Cystine deposition in Kupffer cells is common, and hepatocyte atrophy, regenerative nodules and gastropathy with varices have also been described [122]. Portal hypertension has been reported in the absence of bridging fibrosis [122–124]. Some patients have required portocaval shunting, for esophageal varices and gastrointestinal bleeding, or splenectomy for hypersplenism, thrombocytopenia, leucopenia, and anemia [56].

Exocrine pancreatic insufficiency has been documented in cystinosis [125], indicating that the entire pancreas can be affected. The reported patient exhibited fat malabsorption and responded to pancreatic enzyme supplements.

Treem et al. reported inflammatory bowel disease in a patient with severe cystinosis and multisystemic involvement [126]. Intestinal biopsy revealed crystals in histiocytes of the lamina propria. The deaths of several adult patients have been attributed to intestinal perforation with sepsis or peritonitis [83].

It has been proposed that persistent constipation associated with muscle weakness and failure to thrive could be the first clinical symptom of cystinosis, even before evidence of renal Fanconi syndrome [127]. Early therapy that effectively addresses the mechanical, anatomic, emotional, and behavioral problems associated with feeding can lessen mealtime discomfort and improve the quality of life for affected patients [90].

Late ophthalmic complications Cystinosis eventually affects almost all parts of the eye, particularly the anterior chamber [57]. The cornea becomes hazy by the time the patient is approximately 20 years of age, and a band keratopathy (Fig. 2a) can develop. Chronic photophobia and its resultant squinting can lead to irreversible blepharospasm (Fig. 4c). In addition, many patients develop posterior synechiae, i.e. scar tissue anchoring the posterior lens to the iris. As a consequence, the eye cannot accommodate to light by constriction of the pupil, and this contributes to photophobia. Scarring also predisposes to angle closure glaucoma. In the *Ctns-/-* mouse, cystine crystals accumulate in the tissue surrounding the optic nerve [128], similar to the location of crystals in the pial septa of the optic nerve of cystinotic patients.

In the posterior chamber, the primary area of involvement is the retina, due to loss of retinal pigment epithelia [15]. The first symptoms are poor color vision and impaired night vision, appearing in adolescence or early adulthood with a frequency of approximately 5%. These impairments, considered to be due to damaged rods and cones because of poor nutrient function of the supporting retinal pigment epithelial cells [15], are followed by impaired visual acuity. Electroretinograms document the retinopathy.

Bone involvement Cystinotic patients who have received a renal allograft have several risk factors for developing osteopenia, including crystal deposition in bone, hypothyroidism, primary hypogonadism in male patients, chronic urinary phosphate wasting, renal failure, and prolonged treatment with corticosteroids. In a study, bone mineral density, measured by dual energy X-ray absorptiometry (DEXA), was significantly reduced in both adults and children after transplantation [52], and approximately one-third of patients had multiple fractures. Many patients

developed metabolic bone disease with abnormal microarchitecture on biopsy. In some patients, the DEXA scan was normal, despite a history of frequent fractures, meaning that linear densitometry can be misleading in the diagnosis of bone fragility. Physicians should be aware that osteopenia and bone fragility may occur in cystinotic patients, despite successful kidney transplantation and correction of metabolic mineral losses.

Management of late complications

Diagnostic evaluation Appropriate studies to determine the extent of late extrarenal organ involvement are crucial for optimizing the care of cystinotic patients. For the evaluation of feeding difficulties and swallowing dysfunction, patients should undergo an oral sensorimotor examination and modified barium videofluoroscopy. Poor oral intake with malnutrition requires timely evaluation by a nutritionist for proper caloric intake, food supplementation or parenteral nutrition. Surgical evaluation may be necessary for feeding tube placement in patients who are at risk of aspiration or are malnourished because of severe swallowing difficulties.

Electromyography could be performed to document the myopathy of cystinosis, but muscle atrophy and weakness in a cystinotic patient past adolescence is cystinotic myopathy until proven otherwise. Pulmonary function tests should be performed in all adults, since any degree of myopathy can involve the thoracic musculature. Kidney ultrasound or other radiographic procedures are routinely performed to evaluate renal allografts. Computed tomography or MRI of the brain can reveal cerebral atrophy or basal ganglia and periventricular calcifications. CT of the chest can be used to detect coronary artery and other vascular calcifications. Ophthalmologic examination with electroretinography provides surveillance for late eye complications, including idiopathic intracranial hypertension and retinal dysfunction. Neurological and psychological evaluations should become a regular practice for cystinotic patients, who may develop various neurological and behavioral complications.

In addition to routine blood chemistry tests, laboratory examinations such as a lipid panel, sex hormone levels, and a glucose tolerance test are the minimal tests that should be performed upon initial and follow-up evaluation. Measurement of a leucocyte cystine level in patients receiving cysteamine should be performed routinely for compliance and dose adjustment.

Treatment of symptoms After renal transplantation, the various complications of cystinosis demand attention [129]. Treatment involves insulin, thyroxine and testosterone supplements for patients with diabetes, hypothyroidism and male hypogonadism. An occasional patient will require pancreatic enzyme replacement for steatorrhea due to exocrine insufficiency. Hand tendon transplants have proven beneficial for selected patients with severe distal myopathy. Some patients with hypertension and proteinuria require antihypertensive medications, in particular, angiotensin-converting enzyme (ACE)-1 inhibitors [130]. Growth hormone plays a major role in improving height in cystinotic patients [53], but not after growth plate fusion, which has generally occurred by the time the patient has reached 20 years of age. Supportive pharmacological agents, such as saline eyedrops and proton pump inhibitors, can be used for relief of discomfort associated with cystinosis itself or the side effects of medications.

Cysteamine therapy for late complications The salutary effects of long-term oral cysteamine treatment with respect to renal function [12] have provided hope that cystine-depleting therapy will help preserve non-renal organs as well [131]. Indeed, parenchymal organ (muscle and liver) cystine depletion was apparent in cystinotic patients treated long-term with cysteamine [72]. Moreover, early reports of cysteamine administration to patients with encephalopathy demonstrated almost complete disappearance of their signs and symptoms, including the gross abnormalities on MRI imaging [91].

Recent reports have bolstered the expectation that long-term oral cysteamine therapy can retard or prevent serious late complications of cystinosis. The frequencies of myopathy, diabetes, pulmonary insufficiency, hypothyroidism, hypercholesterolemia, and death decreased with time on cysteamine therapy and increased with time off cysteamine therapy [83]. For example, the mean forced vital capacity (FVC) was 83% of predicted in patients who had received cysteamine therapy for more than 10 years, compared with a mean FVC 54% of predicted for patients who had received cysteamine for fewer than 10 years [83]. Tsilou et al. demonstrated that the frequency of late ophthalmic complications involving the posterior segment of the eye correlated negatively with the duration of cysteamine therapy [15]. This appears reasonable, since orally administered cysteamine should reach the retina via a vascular route [60]. Sonies et al. showed that long-term oral cysteamine therapy helps prevent swallowing impairment (Fig. 5) and feeding difficulties [14]. The vascular calcifications associated with cystinosis occurred far more often in patients who did not receive cysteamine therapy than in those who did [106]. Finally, normal adult height can be achieved by cystinotic patients who receive oral cysteamine therapy from early childhood; we know of several well-treated young adults with heights between 168 cm and 188 cm.

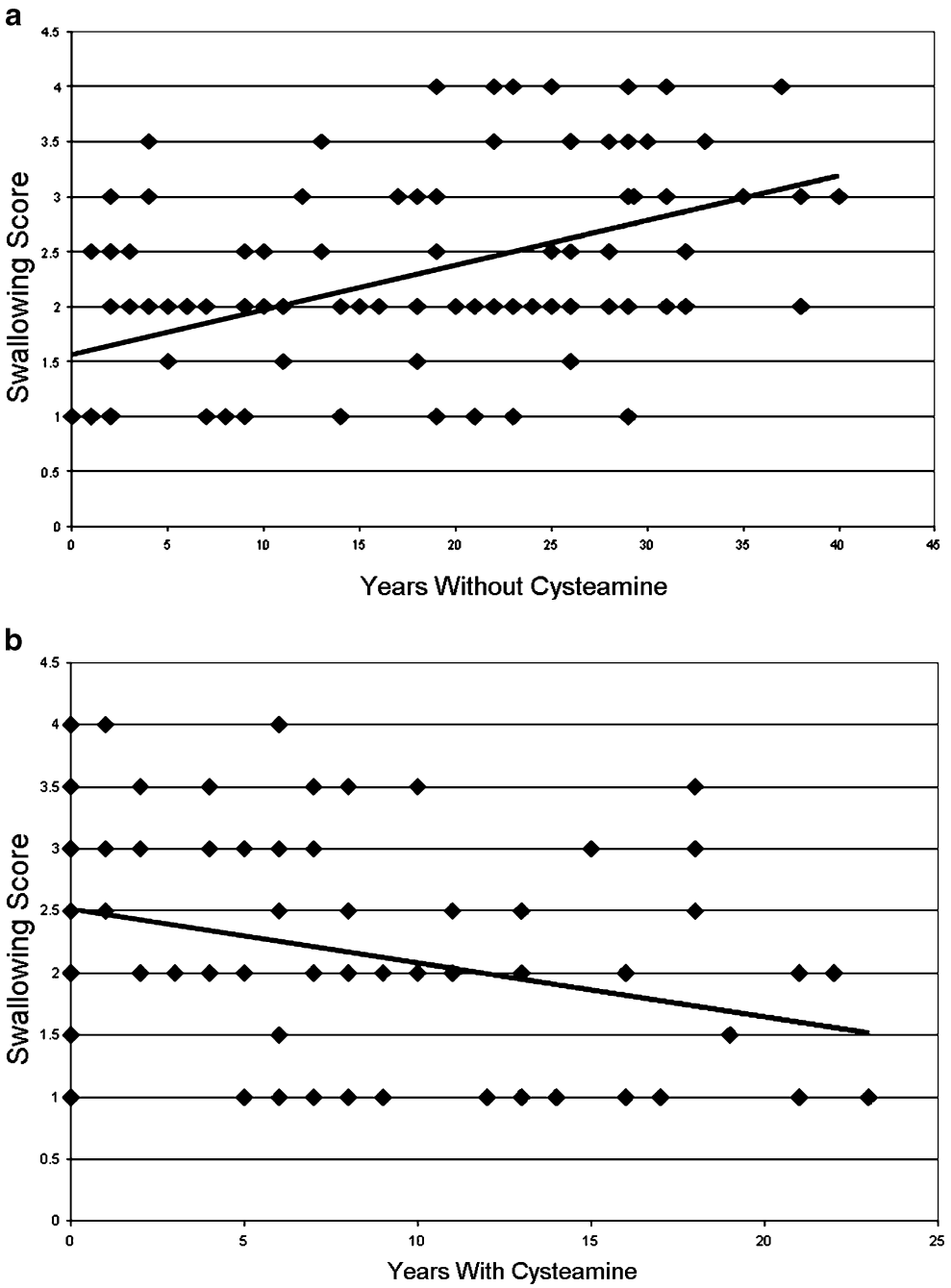

Fig. 5 Swallowing severity score as a function of time without cysteamine treatment **a** and duration receiving cysteamine **b**. The swallowing severity score reflected increasing degrees of dysfunction. On this scale, a rating of 1 indicates a normal bolus flow and duration, a rating of 2 reflects a mild impairment of bolus flow, a score of 3 indicates a moderate impairment of bolus flow with pharyngeal stasis and/or laryngeal penetration, and a score of 4 indicates severe dysphagia with aspiration on more than one bolus consistency and/or a swallow duration longer than 5 s. Swallowing dysfunction increased with years off cysteamine and decreased with years on cysteamine. Reprinted from [14]

The teratogenicity of orally administered cysteamine has not been determined in humans. In rats, very high concentrations impair fetal development [132]. The per-kilogram doses studied were much greater than those that humans take, but women planning to conceive should forego oral cysteamine therapy until after the pregnancy. However, one woman reportedly receiving 300 mg of cysteamine three times a day throughout her pregnancy delivered a healthy infant [133].

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cystinosisfoundation.org/), and the Cystinosis Research Foundation (www.natalieswish.org/) provide advice and support for affected families and funding for research.

Case report

The condition of a 37-year-old Caucasian man was followed at the National Institutes of Health Clinical Center for 22 years. Nephropathic cystinosis was diagnosed when he was 15 months of age, after a classical presentation of Fanconi syndrome; an older brother also carried the diagnosis of cystinosis. Hypothyroidism was treated from 2 years of age, and he suffered growth retardation and photophobia in early childhood. Anemia was present. Chronic renal failure led to an allograft procedure with a cadaveric kidney at 8 years of age. After kidney transplantation, the patient had seizures, transplant dermopathy, atrophy of the upper extremity and proximal trunk muscles, delayed secondary sexual characteristics due to hypogonadism (diagnosed when he was 16 years old), swallowing dysfunction since age 19 years, nicotine addiction since age 21 years, transient ischemic attacks at age 25, malnutrition since age 26, gastrostomy tube insertion due to dysphagia at age 27, obstructive sleep apnea since age 31, and restrictive lung disease diagnosed at age 34 years. Oral cysteamine therapy, initiated at 15 years of age when the leucocyte cystine level was 13.7 nmol half-cystine/mg protein (normal <0.2 nmol half-cystine/mg protein), was undergone poorly for several years but with good compliance for the past decade. Cysteamine eyedrops were administered inconsistently from 15 years to 24 years of age.

Medications included cysteamine bitartrate 2,400 mg a day, L-thyroxine, prednisone, azathioprine, lisinopril, metoclopramide, methyltestosterone, carbidopa-levodopa, fluoxetine, calcium supplements, L-carnitine, calcitonin nasal spray, erythropoietin, ferrous sulfate, coenzyme Q_{10}, a nicotine patch, and multivitamins.

Physical examination at age 37 years revealed an individual of fair complexion and asthenic build (Fig. 6a, b). Height was at the fifth percentile. The patient had hypophonia and dysphasia during oral communication. Vital signs were normal. Neurological examination revealed biceps and triceps tendon reflexes +1 bilaterally, absent Achilles tendon reflexes, a stable gait, and no tremor. Mental status was normal. Findings of a cardiovascular examination were unremarkable. Pulmonary examination showed decreased breath sounds throughout the lung fields bilaterally. Abdominal examination produced normal findings with an intact gastrostomy site. Musculoskeletal examination showed marked muscular atrophy of the hands (Fig. 6c) and upper trunk (Fig. 6d) with decreased strength in the trapezius and shoulder muscles. The thoracic cage had a conical configuration. Results of muscle strength tests gave 2–3/5 in both hands, 4–5/5 in both arms and 5/5 in the lower extremities. Sexual maturation was Tanner stage 5, with testes volume 12 ml. The corneas and conjunctivae were packed with crystals.

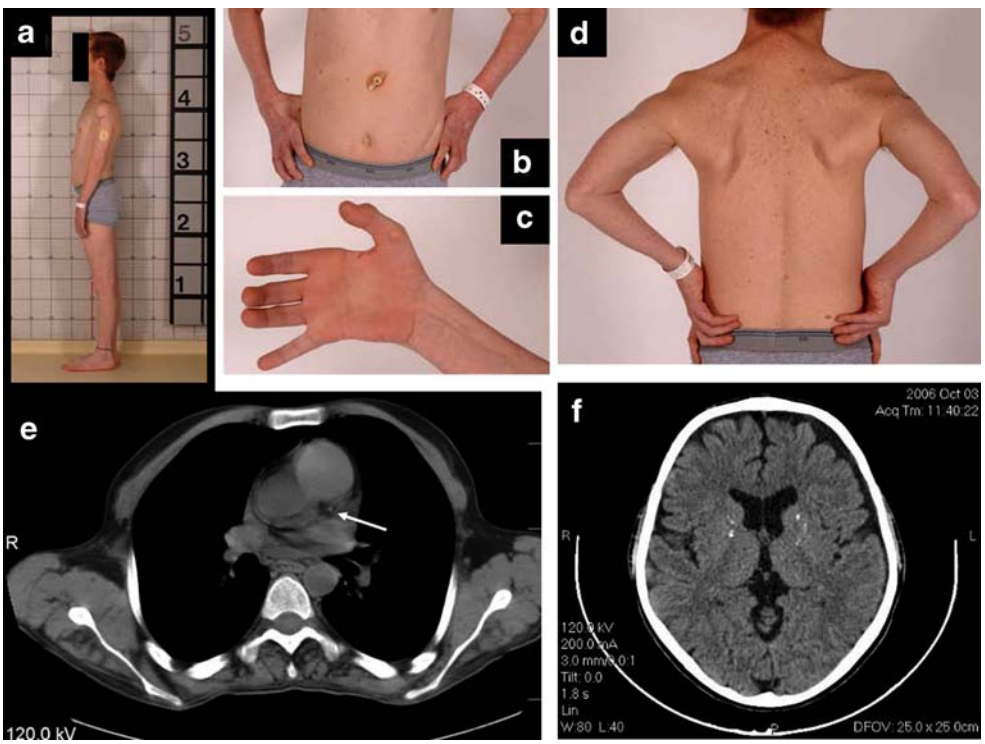

Fig. 6 A 37-year-old man with nephropathic cystinosis, thin habitus **a**, gastrostomy tube **b**, clawed hand with wasting of thenar and hypothenar eminences and interosseous muscles **c**, and muscle wasting in upper trunk **d**. CT scan of the chest **e** shows calcification of the left coronary artery *arrow*. CT scan of the brain **f** shows atrophy and calcifications of the basal ganglia

Laboratory data showed a free thyroxine of 3 ng/dl (normal 0.8–1.9 ng/d), blood urea nitrogen (BUN) 41 mg/dl (normal 8–22 mg/dl), creatinine 2.1 mg/dl (normal 0.9–1.4 mg/dl), corrected creatinine clearance of 22 ml/min per 1.73 m^2 body surface area, free testosterone 0.4 ng/dl (normal 9–30 ng/dl), total testosterone 10 ng/d (normal 240–950 ng/dl), and prolactin 104 μg/l (normal 1–25 μg/l). The 5-h post-dose leucocyte cystine level was 0.94 nmol half-cystine/mg protein. High-resolution chest CT showed calcifications in right and left coronary arteries (Fig. 6e), with no evidence of interstitial lung disease. Pulmonary function tests showed a forced vital capacity of 1.50 l (37% of predicted), a forced expiratory volume in 1 s of 1.22 l (37% of predicted), a vital capacity of 1.50 l (37% of predicted), and total lung capacity of 3.02 l (55% of predicted). Studies of his swallowing revealed moderate to severe oropharyngeal and esophageal dysphagia, conferring a great risk of aspiration. The corneas and conjunctivae were packed with crystals. Computed tomography of the brain identified brain volume loss, prominence of cortical sulci, and abnormal calcifications in the basal ganglia (Fig. 6f).

Recommendations for the patient included increase of his dose of androgens, continuation of oral cysteamine therapy and caloric intake with increased protein and carbohydrates, and re-initiation of cysteamine eye drop therapy. Regular follow-up with a cardiologist was also suggested.

Conclusions

Significant progress has been achieved in recent decades in the understanding of cystinosis and its late complications. The course and severity of the disease, as well as the therapeutic efficacy of cystine-depleting agents, are influenced by genetic heterogeneity. Cystinosis is eminently treatable, and most of its complications are preventable with cysteamine therapy; early detection is essential for effective treatment. Optimal care requires a team of nephrologists, metabolic disease specialists, genetic counselors, and other sub-specialists. The establishment of centers specializing in cystinosis will improve considerably the care and quality of life for patients. In the future, the development of a screening test for cystinosis in newborn infants would allow physicians to achieve a new level of therapeutic success for this disease.

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