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# Infantile Cystinosis

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## ABSTRACT

Infantile cystinosis is a rare disorder which left untreated results in end-stage renal disease early in life. Together with dehydration and electrolyte imbalance due to renal tubular Fanconi syndrome, end-stage renal disease used to be the leading cause of death in children with cystinosis. Specific therapy with cysteamine (cystine-depleting agent) has changed the course of this disease. Instead of being fatal in childhood, it can nowadays be considered a multisystemic adult disorder. The authors report a case of a child diagnosed with Fanconi syndrome at 14 months of age and infantile cystinosis at 19 months of age in whom oral cysteamine treatment led to a good outcome during childhood.

**Key-Words:**
Cystinosis; cysteamine; end-stage renal disease; lysosomal disease.

## INTRODUCTION

Cystinosis is a rare autosomal recessive lysosomal storage disorder caused by impaired transport of the amino acid cystine from cellular lysosomes. It has an estimated annual incidence of 1 case per 100,000 to 200,000 live births and the causative gene, CTNS, mapped in chromosome 17p13, encodes the protein cystinosin[1,2]. Early findings of the classic infantile form include Fanconi syndrome, rickets, impaired growth, hypothyroidism and corneal crystals[1-4]. Without specific therapy, deterioration of the renal function results in renal failure in the first decade of life[2]. Specific therapy with cysteamine has proven efficacious. By inhibiting the accumulations of cystine, it not only prevents or delays renal deterioration, but also enhances growth, heals rickets and prevents several of the early and late non-renal complications of cystinosis[2].

In this article the authors report a case of infantile cystinosis with a good clinical outcome.

## CASE REPORT

A Caucasian boy, with no known family history of cystinosis, product of a non-consanguineous union, was delivered after a full-term uneventful pregnancy. He had a normal birth weight and height. By 6 months of old, nappy rash and a change in urine smell motivated several urinalyses. He was presented to the paediatric nephrology outpatients department at 14 months old with persistent glycosuria. At this time, with a proper caloric intake, he was found to have growth under percentile five, widening of the wrists and *genus valgus*, without any other clinical symptom or sign. Laboratory investigation established the diagnosis of Fanconi syndrome with polyuria, loss of glucose, phosphate, calcium, uric acid and amino acids in the urine, metabolic acidosis, with a normal anion gap, and an HCO3 urinary excretion fraction of 14%. The bone age was equivalent to a child of six months. He was started on supportive therapy with sodium and potassium citrate, phosphate, calcitriol and indomethacin with clinical, laboratory and radiology improvement. At

the age of 19 months, a leucocyte cystine measurement of 3.2 nmol half-cystine per mg protein set the diagnosis of cystinosis. In the DNA assay, a homozygotic 57-kbA deletion in the CTNS gene was found. Specific therapy with phosphocysteamine, which was later replaced by cysteamine at a dose of 60mg/Kg of body weight per day, given every six hours, was started. Aiming to maintain cystine levels below 1.0 nmol half-cystine per mg protein, cysteamine dose was adjusted according to yearly leucocyte cystine measurements. During the following years, until his present age of 18 years old, there was a progressive improvement of his bone deformities and his growth proceeded near the 25$^{th}$ percentile. He had a normal pubertal development and thyroid hormones and transaminases remained in the normal ranges. At the age of two years old he appeared with complaints of photophobia. Corneal cystine crystals were manifest and topical cysteamine therapy started. Due to low compliance, he maintained photophobia complaints until he was 14 years old. At the present time he has no crystals in the cornea. The glomerular filtration rate (GFR) was normal until the age of 17, with a present value of 60 ml/min/1,73m$^2$. Renal ultrasound has shown kidney stones and increased cortical echogenicity since the age of 11 years old. At the age of 15 years he was submitted to a bilateral proximal tibial epiphysiodesis to correct *genus valgus* with sucess.

## DISCUSSION

Renal manifestations dominate the clinical presentation and course of infantile cystinosis[3]. Our patient was normal at birth and the typical poor growth and rickets were detected by 14 months. At this age he was diagnosed with Fanconi syndrome and rickets, which is the classic presentation of cystinosis and occurs in 95% of the cases between the sixth and twelfth month of life[1,3]. The leucocyte cystine measurement set the diagnosis and the homozygotic 57-kbA deletion in the CTNS gene detected is the most common mutation causing the classic form of this disorder[4].

In the absence of specific treatment, creatinine clearance decreases inexorably and end-stage renal disease develops in the first decade of life[1,5]. In these cases, renal transplantation is life saving and disease does not recur in the kidney if native kidneys are extirpated[2,6]. Nevertheless, cystine storage continues in non-renal tissues[2,6]. Instead, long term oral administration of cysteamine addresses the cause of the disease, depleting the cells of 95% of their cystine content[7]. Therefore, when introduced early in the course of the disease and taken diligently, cysteamine can accomplish the preservation of renal function and allow a normal growth rate[4,7,8]. Cysteamine also prevents non-renal early complications of cystinosis as hypothyroidism[8]. Indeed, in the reported case, with the introduction of cysteamine at 19 month of age, renal function was preserved until the age of 17, linear growth increased dramatically, with a significant improvement of height velocity, and hypothyroidism was avoided. To achieve these targets an adequate replacement of renal losses, an early and long term treatment with oral cysteamine and frequent leucocyte cystine measurements were required. These determinations allow cysteamine dose adjustments and evaluation of therapy compliance.

Regarding ophthalmic manifestations, crystal accumulation in the conjunctiva and cornea, with photophobia and pigmentary retinopathy, are the earliest complications[10]. In this case, corneal cystine crystals became symptomatic at the age of two years. Oral cysteamine do not dissolve corneal cystine crystals but, as published in the literature, therapy with frequent topical cysteamine eye drops has completely dissolved the crystals[11].

The renal transplant and specific therapy with cysteamine transformed cystinosis into a chronic treatable disease. At this moment our patient has no symptomatic late extra renal complication. Nevertheless, with the much longer life span achieved, late complications of the disease may come to light. Among them are progressive myopathy, central nervous system disease, arterial hypertension and cardiomyopathy, diabetes, hypercholesterolemia and hepatic and pulmonary involvement[6,8,9].

## CONCLUSIONS

This case illustrates the efficacy of therapy with oral cysteamine in delaying renal deterioration, enhancing growth and preventing early non-renal

complications of cystinosis. To achieve these targets, early diagnosis, good therapy compliance and frequent dose adjustments are crucial. With the resulting longer life expectancy, the clinical course of cystinosis has changed from a mainly renal disease to a multisystemic disorder with new therapeutic challenges. Recent reports show that the frequency of diabetes mellitus, myopathy, pulmonary dysfunction, hypothyroidism and death decreased as time on cysteamine therapy increased, and increased with time off cysteamine treatment[9]. Despite diligent oral cysteamine therapy, cysteamine hydrochloride eye drops given 10-12 times per day are required to relieve photophobia within weeks and dissolve corneal crystals within months.

***Conflict of interest statement.*** None declared.

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