CASE REPORT

Infantile Nephropathic Cystinosis: Diagnosis and Treatment of a Systemic Disease

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Abstract

Cystinosis is a rare autosomal recessive lysosomal storage disorder leading to end-stage renal disease and many extra-renal complications. This is a case of a 17-month-old girl who showed normal development until 14 months when her parents noted polydipsia, polyuria, and growth stagnation. Investigations performed in a tertiary setting were compatible with Fanconi syndrome and radiography with rickets. The hypothesis of diagnosis of infantile nephropathic cystinosis was raised. The high intra-leukocytic cystine and the genetic study confirmed the disease. Treatment with cysteamine was started. At 21 months, cystine eye crystals appeared and topical cysteamine was added. She is currently 3 years old with a satisfactory weight and height progression, stable kidney disease, without the progression of rickets, and has asymptomatic eye crystals.

A high degree of suspicion for this disease allows for an early start of targeted therapy and an adequate follow-up, improving the prognosis of a disease with high morbidity.

Keywords: Cysteamine/therapeutic use; Cystinosis/complications; Cystinosis/diagnosis; Cystinosis/therapy; Fanconi syndrome/diagnosis; Fanconi syndrome/etiology; Fanconi syndrome/therapy; Kidney Diseases; Treatment Outcome

Introduction

Cystinosis is a rare, autosomal recessive disease that is caused by mutations in the *CTNS* gene, encoding cystinosin.[1-4] Its deficiency results in early lysosomal cystine accumulation in virtually all tissues.[1-3,5] There are three different forms, depending on the severity of mutations: infantile nephropathic cystinosis, juvenile nephropathic cystinosis, and non-nephropathic cystinosis.[6] The general incidence of the disease is 1:100,000-1:200,000 live births.[1,2,4,7]

The kidney is the first affected organ and infantile nephropathic cystinosis is the most frequent and severe form, affecting about 95% of patients.[1,3,5,7] In infantile nephropathic cystinosis, children appear normal at birth, but by 6-18 months of age, renal Fanconi syndrome develops.[1-5,7] In addition, the glomerular filtration rate remains normal up to 2 years of age, but by 5-6 years of age it begins to deteriorate and end-stage kidney disease is reached by 10 years of age.[1-3,5,7]

The first manifestation is asymptomatic hyperaminoaciduria.[3] Then, selective proximal tubular dysfunction develops, with excessive urinary loss of sodium, potassium, bicarbonate, magnesium, carnitine, calcium, phosphate, glucose, and proteins, manifested by polyuria, polydipsia, episodes of severe dehydration and electrolyte imbalance, failure to thrive, vomiting, constipation, weakness, unexplained fever, and vitamin D resistant rickets.[2,3,7]

The eye is the second affected organ and cystine crystals are found in the cornea and retina from the age of 12 months, potentially causing severe photophobia, blepharospasm, recurrent painful corneal erosions and progressive retinopathy, leading to blindness.[1-3] Nearly all nephropathic cystinosis patients who did not receive cystine-depleting therapy develop major extra-renal manifestations, like growth retardation, hypothyroidism, hypogonadism, endocrine and exocrine pancreatic insufficiency, hepatomegaly, splenomegaly, myopathy, rickets, bone deformities and fragility, and neuromuscular and neurocognitive disfunction.[1-3]

The detection of the corneal cystine crystals by slit lamp examination, elevated intra-leukocytic cystine levels, and molecular testing of the *CTNS* gene make the diagnosis of cystinosis.[3,5]

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Cysteamine is an oral cystine-depleting drug, the only target-specific therapy available, and should be started as soon as possible and continued lifelong.[1-3] With the exception of established Fanconi syndrome and male infertility, it delays or prevents other extra-renal complications, improves growth and prolongs kidney function survival, achieving end-stage kidney disease by 20 years of age, instead of 10.[1-3,5] A new cysteamine formulation with delayed-release simplifies the administration schedule but still does not cure infantile nephropathic cystinosis.[6]

We describe a case of infantile nephropathic cystinosis in a 17-month-old girl, presented with Fanconi syndrome, and her evolution until 3 years old.

Case Report

A 17-month-old girl, second daughter of a non-consanguineous couple, with an uneventful pregnancy and delivery, with an adequate development until 14 months and no other relevant antecedents. There was no relevant past family history of kidney, ophthalmic, neurological or bone diseases as well as developmental delays or history of early death.

The first symptoms occur by 14 months of age, when parents detected polydipsia, polyuria, and weight stagnation, with no other signs or symptoms. Complete blood count and urinalysis performed at the pediatrician at 15 months revealed no changes, but those performed at 17 months, three days before going to the emergency department, showed hypokalemia (2.6 mmol/L), decreased urinary ions (sodium 17 mEq/L, potassium 10.7 mmol/L, chloride 28 mmol/L), leukocyturia (+++), proteinuria (+), and glycosuria (+), with no other information.

She was referred to an emergency department of a level III hospital where, on admission, she was dehydrated, with a diaper erythema. An analytical evaluation revealed a stage GIIIb chronic kidney disease - estimated glomerular filtration rate (eGFR) 37.3 mL/minute/1.73 m^2) - with hyponatremia (129 mmol/L), hypokalemia (2.8 mmol/L), hypophosphatemia (3 mg/dL), hyperchloremia (110 mmol/L), and metabolic acidosis (bicarbonate 15 mmol/L). Urinary analysis revealed a proximal renal tubular disfunction (glycosuria of 100 mg/dL, without hyperglycemia and proteinuria of 25 mg/dL), with excessive ion excretion and a lack of ion reabsorption (density 1005, fractional excretion of sodium 2%, fractional excretion of potassium 42%).

The main diagnostic admitted was renal Fanconi syndrome and the girl was hospitalized for treatment and clarification of the etiology.

Conservative therapy for chronic kidney disease was quickly started with sodium bicarbonate, potassium chloride, sodium chloride, phosphorus, iron, folic acid, erythropoietin, and cholecalciferol, progressively adjusted, with improvement in the analytical parameters. High blood pressure was also diagnosed. The evaluation by the pediatric cardiology ward excluded major heart changes, and antihypertensive therapy with enalapril and amlodipine was started. A personalized and supplemented diet with a food fortifier and an unrestricted water supply was also added. She was discharged on the 15th day of hospitalization, clinically and analytically improved, maintaining the therapy initiated and referred to a multidisciplinary follow-up.

The investigation of Fanconi syndrome in the context of infantile nephropathic cystinosis was completed on an outpatient basis. The intra-leukocytic cystine level was shown to be high, 0.46 µmol/g of protein (reference values 0-0.3 µmol/g of protein), and the genetic study revealed the c.614_616delACG (p.D205del) mutation, confirming the disease. The ophthalmologic evaluation did not show deposits of cystine crystals in the cornea at that time. Nephrology evaluation also showed no other changes. However, the radiographs of the extremities of the limbs showed rickets, namely irregular bony edges, with a dome sign and fraying and cupping of metaphysis (Fig. 1). Therapy with systemic cysteamine, 1 g/m^2/day, every six hours, was started at 18 months and, at 21 months, due to cystine crystals deposits in the left eye, cysteamine eye drops 3.8 mg/mL with one drop every six hours was added. Symptomatic therapy was regularly adjusted.

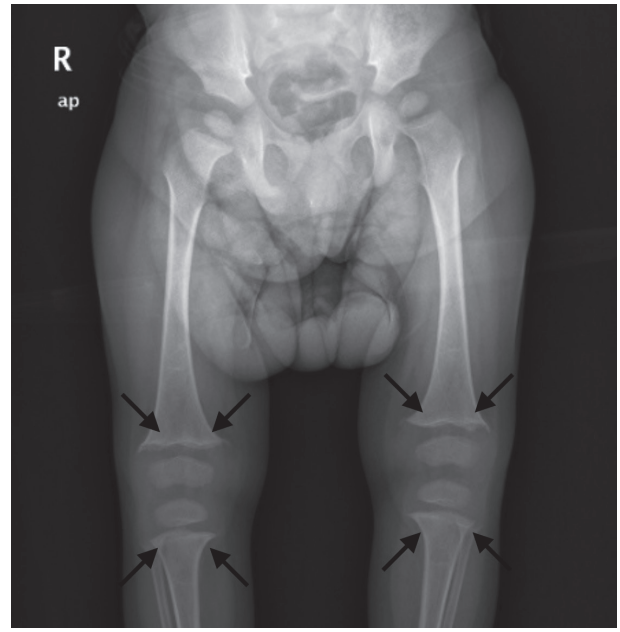


Figure 1. Radiography of the long bones of the lower limbs showing signs of rickets, identified with arrows, and genu varum.

At 3 years old, the girl is clinically stable (Figs. 2, 3, and 4). There was a weight progression mainly at the 15th-50th percentile for sex and age as well as a height progression at the 3rd-15th percentile, with no neurological or behavioral manifestations. Regarding blood pressure, a normal stage was reached under therapy, with no cardiac involvement. From the ophthalmological point of view, there was also a quantitative improvement in the ocular cystine crystal deposits after starting topical therapy, which currently is with crystals only in the anterior stroma, without reaching the posterior stroma (Fig. 5) and without photophobia. She maintains an asymptomatic *varus* of the knees, requiring only a clinical annual assessment. She presents a normal intra-leukocytic cystine value now. She is still in stage G3b of chronic kidney disease but with a progressive improvement in blood tests related to the degree of hydration (last eGFR 118.4 mL/minute/1.73 m^2). The associated imbalances are controlled, such as acid base balance, ionic balance, and phosphocalcic metabolism. Regarding the endocrinological system, the thyroid function and glucose metabolism are normal. The liver function also remained stable and no other changes are observed.

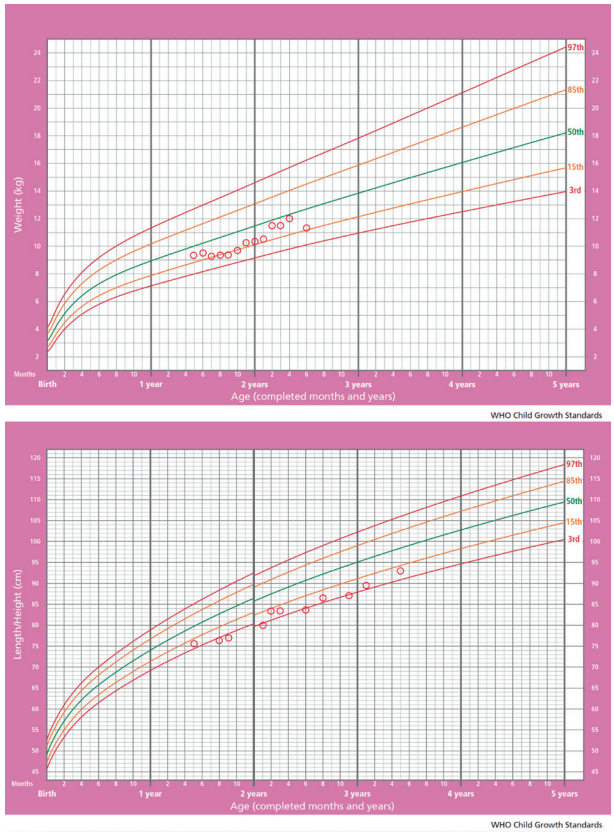
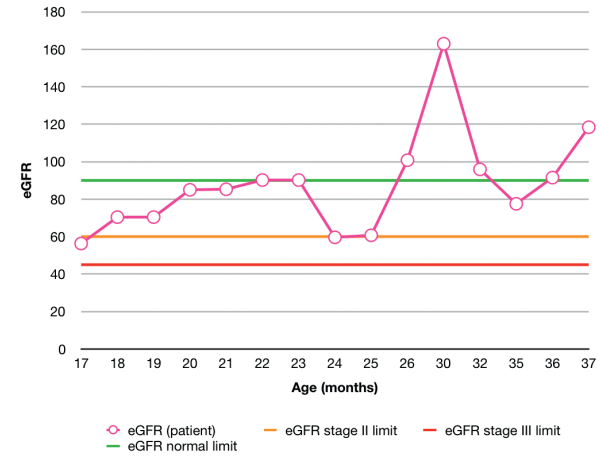
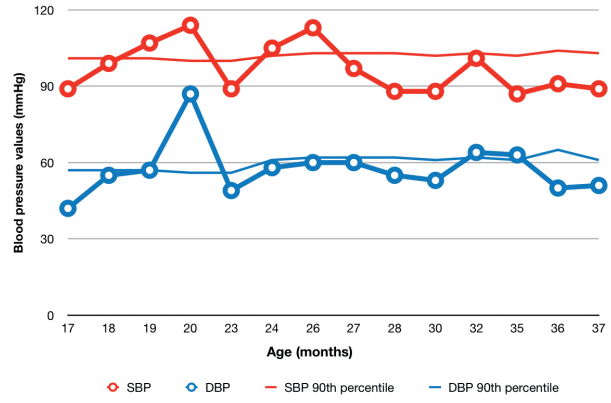


Figure 2. Evolution of weight and height from 17 to 41 months of age.



eGFR - estimated glomerular filtration rate.

Figure 3. Evolution of the estimated glomerular filtration rate from 17 to 37 months of age.



DBP - diastolic blood pressure; SBP - systolic blood pressure.

Figure 4. Evolution of systolic and diastolic blood pressure from 17 to 37 months of age.

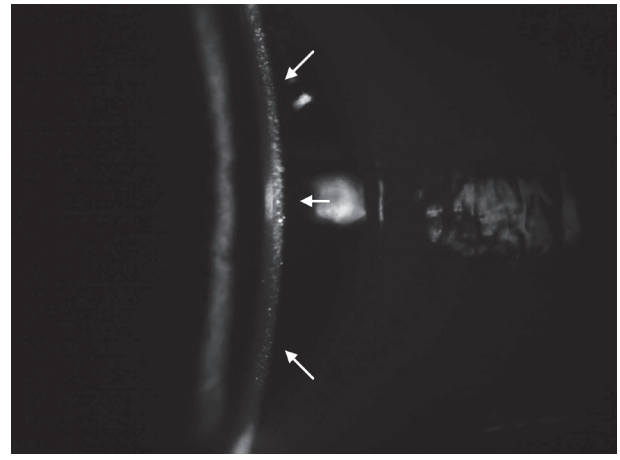


Figure 5. Slit lamp photography of the anterior segment of the eye showing crystals of cystine in the corneal anterior stroma (white arrows).

Discussion

Infantile nephropathic cystinosis is the leading cause of inherited renal Fanconi syndrome, but it is a rare disease and, therefore, a high degree of suspicion in necessary.[1-4] Due to the availability of cysteamine, early diagnosis and management of this disease have a great impact on the clinical outcome.[3]

The proximal tubular dysfunction is represented by the metabolic acidosis, glycosuria without hyperglycemia, proteinuria, and phosphaturia. In the acute situation, no more analytical data were requested, as they would not add information that would change the therapeutic attitude or the diagnostic hypothesis and the primacy was to stabilize the patient, with fluid and replacement therapy (biasing the ionic calculations thereafter).

The diagnosis of cystinosis is genetic and the mutation found in this patient (c.614_616delACG) is one of the mutations responsible for the infantile phenotype of infantile nephropathic cystinosis and it was previous described in 1998 in the US and in 1999 in the UK.[1]

In this case report, early diagnosis enabled the early initiation of the therapy with cysteamine as well as the implementation of an appropriate multidisciplinary follow-up. The regular evaluation by ophthalmology allowed the early detection of cystine crystals, even in an asymptomatic period, and an early initiation of the targeted treatment with cysteamine eye drops. Nevertheless, some systemic manifestations will develop later and, therefore, the multidisciplinary follow-up should remain regular.

Concerning the oral therapy, both extended- and immediate-release cysteamine have been proven to reach the cystine target levels that are thought of as necessary to slow down the progress of cystinosis-related symptoms.[6] Immediate-release oral formulation demands a strict six hours administration schedule while the extended one must only be administered twice daily, thereby simplifying the administration schedule and supporting therapy adherence.[6] Nevertheless, cysteamine is associated with some adverse effects, such as bad sweat odor, halitosis, nausea, dyspepsia, vomiting, epigastric pain and, rarely, hyperthermia, lethargy, neutropenia, seizures, and allergic rash.[2,3] In this case report, extended-release therapy has not yet started because there is still no authorization for its use in children, thereby hindering the therapeutic regimen, and the patient has no side effects. Concerning topical therapy, cysteamine eye drop formulation is an aqueous solution, which needs to be administered 6-12 times per day, and it is unstable at room temperature and to light exposure, complicating storage, transport, and adherence.[8] It is also associated with a topical burning sensation.[3] A new gel-like viscous topical formulation, with fivefold higher concentration of cysteamine, has been developed and has to be administered only four times daily.[6] It increases the contact time to cornea, allowing the cysteamine to penetrate more deeply into the corneal layers, but it can also increase the side effects.[6] In this case, the commercial gel-like formulation was started and the girl presents no side effects.

Supportive treatment is also important to maintain an adequate fluid, electrolyte and acid-base balance, provide nutritional support, prevent the development of rickets, ensure adequate hormonal replacement, and control late complications.[3,5,9] Renal, bone marrow-derived cells and hematopoietic stem cells transplantation could be also necessary, although there are considerable risks of morbidity and mortality.[1-3,5] A future perspective offering a curative therapy may be the transplantation of *CTNS*-carrying stem cells.[6]

Despite the therapeutic strategy, the treatment enables patients to reach adolescence, arising new problems with therapy adherence at this age, and special transition protocols to adult health-care services are recommended.[6] Genetic counseling is also essential and prenatal diagnosis is possible.[9] Even though the depleting therapy with cysteamine - oral and topical - has dramatically improved life expectancy of cystinosis patients, namely the new formulations that alleviate the medical schedule and support therapy adherence, it is still not a curative therapy because the defective lysosomal transport protein cystinosin is only bypassed.[6] Moreover, it does not treat established Fanconi syndrome and that is why conservative therapy is crucial.[1-3,5] The hypertension presented may also be related to the kidney disease and should be treated and controlled to not aggravate kidney disease or cause injury in other target organs.

The long-term prognosis of patients with infantile nephropathic cystinosis has dramatically improved during the last 30 years.[1,3] Nevertheless, the combination of cysteamine therapy and multisystemic supportive treatment requires many daily medications.[2-5] The severity of renal Fanconi syndrome, the resistance and important side effects of cysteamine, the multi organ involvement and other key functions that *CTNS* exerts, point out the necessity of developing new treatments.[1,3-5]

A myriad of unsolved questions remain to be answered, specifically the unique features in proximal tubular cells that explain their early vulnerability, the molecular mechanisms that account for the development of proximal tubular cells dysfunction before the

development of detectable lesions, the many cellular and molecular mechanisms in which cystinosin interferes, and how best to translate this knowledge into better management.[2] Since infantile nephropathic cystinosis is a multi-systemic disease, gene therapy is challenging, but a combination of genomic, proteomic, and metabolic approaches could lead to new therapeutic approaches and potentially cure this disease.[1,2] Until then, the diagnosis must be early with a high degree of suspicion and the targeted therapy started early with what is currently available: cysteamine.

WHAT THIS CASE REPORT ADDS

- With this case report, we intend to demonstrate the importance of thinking about some rare diseases during the normal clinical practice. This way, it is possible to use unusual blood tests, as intra-leukocytic cystine or genetic tests, and start targeted therapy early, being able to reverse some of the manifestations and delay the appearance of new ones.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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This case report was presented at the 16th International Symposium of Portuguese Society for Metabolic Disorders held in Lisboa, Portugal, 2020.

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Cistinose Nefropática Infantil: Diagnóstico e Tratamento de uma Doença Sistémica

Resumo

A cistinose é uma doença autossómica recessiva rara que origina doença renal terminal e várias complicações extra renais. Menina de 17 meses, com um desenvolvimento adequado até aos 14 meses, quando os pais notaram polidipsia, poliúria e crescimento desadequado. A investigação realizada num centro hospitalar terciário foi compatível com síndrome de Fanconi e a radiografia com raquitismo. A hipótese diagnóstica de cistinose nefropática infantil foi colocada. O nível elevado de cistina intraleucocitária e o estudo genético confirmaram a doença. O tratamento com cisteamina foi iniciado. Aos 21 meses, surgiram cristais oculares de cistina e adicionou-se cisteamina tópica. Atualmente, com 3 anos, a doente apresenta uma progressão estaturo-ponderal adequada, com doença renal crónica estável, sem progressão do raquitismo e com cristais oculares assintomáticos. O elevado nível de suspeição para esta doença permitiu o início precoce de terapêutica dirigida e o acompanhamento adequado, melhorando assim o prognóstico desta doença, com elevada morbilidade.

Palavras-Chave: Cisteamina/uso terapêutico; Cistinose/complicações; Cistinose/diagnóstico; Cistinose/tratamento; Doenças do Rim; Síndrome de Fanconi /diagnóstico; Síndrome de Fanconi/etiologia; Síndrome de Fanconi/tratamento; Resultado do Tratamento