



Submitted on: 01/25/2024

Approved on: 11/27/2024

CASE REPORT

Nephropathic cystinosis: case report that reflects the importance of the disease

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Keywords:

Cystinosis,
Fanconi Syndrome,
Cysteamine,
Kidney Failure
Chronic.

Abstract

Introduction: cystinosis is a lysosomal storage disease, caused by a mutation in the CTNS gene, which encodes cystinosin, a protein responsible for the transport of cystine in the lysosome membrane. The disease is manifested by marked tubular dysfunction and Fanconi syndrome, including polyuria, polydipsia, growth retardation and rickets. We report a classic case of nephropathic cystinosis. **Case report:** patient aged 1 year and 6 months, female, referred for investigation of polyuria, polydipsia and low weight gain. Upon admission, she presented metabolic changes, symptoms compatible with Fanconi syndrome, rickets and short stature. **Discussion:** considered a rare disease, cystinosis manifests as Fanconi syndrome, and when early diagnosed and treated, progression to chronic kidney failure can be delayed.

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INTRODUCTION

Cystinosis is a rare disease caused by a mutation in the CTNS gene, leading to a defect in lysosomal transport and consequent deposition of cystine in different organs and tissues. Infantile cystinosis is the most common form of the disease, affecting one in every 100 to 200 thousand children. It presents in the first two years of life, with severe tubular dysfunction and growth retardation¹.

Clinical manifestations reflect severe tubular dysfunction and Fanconi syndrome, including polyuria, polydipsia, growth retardation and rickets. Fever is common, caused by dehydration or decreased sweat production. Ocular manifestations include keratitis, with photophobia and impaired visual acuity¹.

Diagnosis is suggested by the detection of cystine crystals in the cornea and confirmed by determination of increased leukocyte cystine content. Treatment is directed at correcting the metabolic alterations associated with tubulopathy and specific therapy with cysteamine, which binds to cystine, facilitating lysosomal transport through alternative pathways¹.

CASE REPORT

A one-year-and-six-month-old female infant was admitted to a university hospital in the city of Rio de Janeiro for investigation of polyuria, polydipsia, and weight and height deficit, which began in the second half of life. The mother reported weight loss of approximately 10% in one month. Despite being very low in weight and height for her age, she did not have significant delays in neuropsychomotor development. She also had chronic constipation.

The 21-year-old mother reported that this was her first pregnancy, with no complications during prenatal care, and she was unaware of her prenatal serologies. The patient was born by cesarean section at the mother's request, at a gestational age of 39 weeks, with an Apgar score of 9/10, and no need for neonatal resuscitation. The patient weighed 3,398 grams, had a length of 48 cm and a head circumference of 36 cm. The neonatal screening tests were within normal limits.

The patient was exclusively breastfed until she was 6 months old and, when she was introduced to solid foods, she noticed that she had difficulty accepting foods and that she was drinking more water. She had not been hospitalized before and had no history of allergies.

Upon admission, the patient was very low in weight and height for her age (z score: < -3), with an adequate head circumference and a body mass index (BMI) indicating normal weight (z score -1 and -2). On physical examination, she was in good general condition, emaciated, pale, dehydrated, and had adequate interaction and language for her age. Wide anterior fontanelle, motor coordination was present and tone was reduced, but strength was preserved. Pulmonary and cardiovascular auscultation showed no abnormalities. Abdomen was rounded with splenomegaly. Limbs were

symmetrical. Skin, nails and hair were normal. Laboratory tests showed the following alterations: metabolic acidosis, anemia, hyponatremia, hypokalemia, hypomagnesemia, hypophosphatemia, elevated alkaline phosphatase and increased parathyroid hormone (PTH); and normal renal function. Urine tests showed glycosuria with normal blood glucose, proteinuria and elevated $\beta 2$ -microglobulin levels. Initial suspicion of tubular disease associated with Fanconi syndrome. The bone age radiograph was compatible with nine months and the long bone radiograph (figure 2) showed

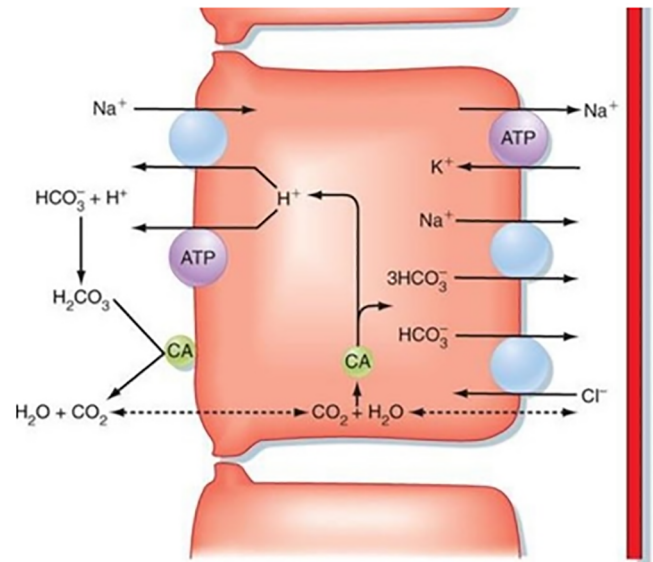


Figure 1. Mechanism of reabsorption in the proximal convoluted tubule.



Figure 2. radiograph. Source: author.

irregularity of the endochondral growth line due to probable calcium mobilization. Considering that one of the main causes of Fanconi syndrome in this age group is cystinosis, we requested an ophthalmological evaluation, which showed cystine deposits in the cornea (figure 3).

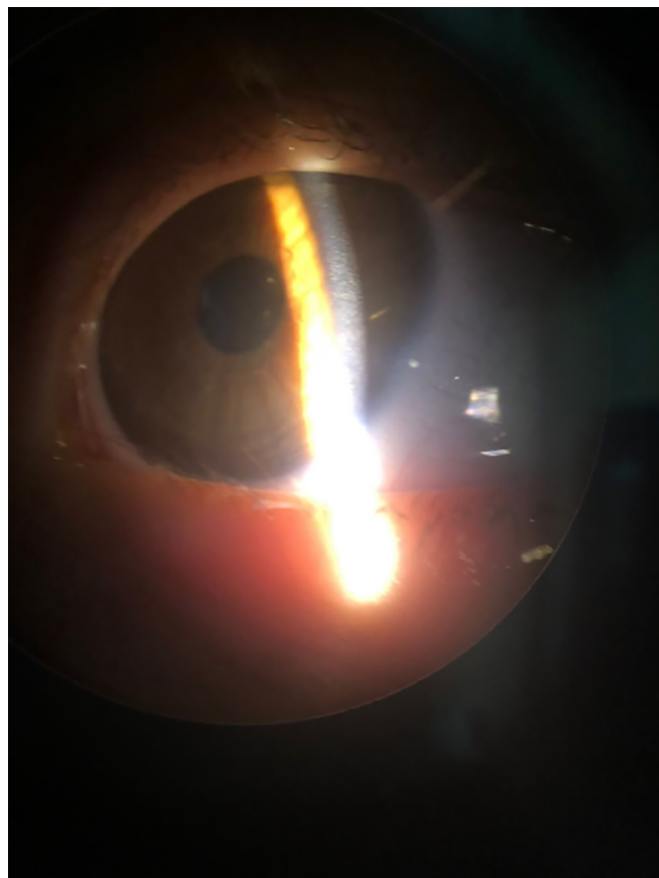


Figure 3. Ophthalmological evaluation. Source: The Author.

DISCUSSION

Cystinosis is a rare lysosomal storage disease caused by a mutation in the CTNS gene, which encodes cystinosisin, a cystine transport protein that functions as a proton symporter. Therefore, when there is a change in this protein, cystine deposits occur in organs and tissues. It is one of the genetic conditions associated with Fanconi Syndrome¹⁻⁸.

To understand the clinical manifestations and metabolic changes of the disease, it is important to understand the mechanisms of renal filtration, secretion and reabsorption. The tubular portion of the kidney acts on the acid-base balance through the reabsorption of bicarbonate and excretion of H⁺ ions. Part of this process occurs in the proximal tubule cell (figure 1) – the H₂O molecule combines with CO₂ to form H₂CO₃, which quickly dissociates into H⁺ and HCO₃⁻ through the enzyme carbonic anhydrase II. Na-K-ATPase, in the basolateral membrane, generates an electrochemical gradient within

the cell leading to the reabsorption of sodium from the lumen. In the lumen, H⁺ combines with filtered HCO₃, resulting in H₂CO₃, which is broken down into water and CO₂ by carbonic anhydrase IV. The CO₂ generated in the lumen then returns to the cell through the AQP1 channel. For each H⁺ ion secreted, one bicarbonate molecule is reabsorbed across the membrane into the circulation. Thus, the proximal tubule is responsible for reabsorbing approximately 90% of the filtered bicarbonate^{2,4}. Abnormalities in this process are characteristic of some genetic forms such as mutations in carbonic anhydrase, NHE3 and genetic Fanconi syndrome.

The patient in this case began to present with polyuria and polydipsia, presenting glycosuria in the urine test - with normal plasma glucose concentration -, proteinuria, high β 2-microglobulin titers and metabolic acidosis. These alterations, as well as renal phosphate loss, are characteristic of proximal tubule dysfunction. One of the consequences of these alterations is rickets. The patient presented increased PTH and alkaline phosphatase and hypophosphatemia. Radiographs of the wrist and long bones showed delayed bone age and rickets, respectively.

In addition to these symptoms, the disease can manifest with photophobia, keratitis and impaired visual acuity. Patients can also develop hypothyroidism, hepatosplenomegaly and delayed sexual maturation.

Depending on the severity of the renal disease, the phenotype of cystinosis presents three clinical forms. Nephropathic infantile cystinosis affects approximately 95% of patients and is characterized by Fanconi syndrome during the first months of life. The mild form of the disease manifests in adolescents and is characterized by less severe tubular abnormalities and slower progression to renal failure. Lastly, non-nephropathic cystinosis is a benign or ocular variant of the disease in adults without renal involvement^{1,5}.

The diagnosis of the patient in question was made through a simple ophthalmological examination using a slit lamp, which detected cystine crystals in the cornea.

Treatment begins with the correction of hydroelectrolytic disorders, nutritional support and prevention of rickets. Specific treatment is with cysteamine, whose molecule can be combined with half a cystine molecule (cysteine) to facilitate the release of cystine from the lysosome. It should be started as soon as the diagnosis is confirmed, as it preserves renal function, prevents hypothyroidism and improves growth in affected children. Administration of cysteamine directly treats the disease, reducing the intracellular cystine content. Cysteamine enters the cell and is concentrated within the lysosomes, where it reacts with cystine to form cysteine-cysteamine, which is capable of leaving the lysosome⁵⁻⁷. Oral cysteamine does not produce adequate levels in ocular tissues, making additional therapy with cysteamine eye drops necessary.

The natural history of cystinosis is progression to kidney disease in the first ten years of life. The long-term prognosis of patients with this diagnosis has improved dramatically in

recent years due to the availability of the drug cysteamine and advances in kidney transplantation⁹. In Brazil, cysteamine is still a substance that is difficult to access. Obtaining it requires a purchase request through legal proceedings, which delays the patient's treatment and worsens their prognosis in relation to kidney function. On the other hand, timely diagnosis of the disease allows the correction of metabolic disorders and the recovery of the child's growth and development, improving their quality of life.

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