SQU Med J, November 2011, Vol. 1, Iss. 4, pp. 503-506, Epub. 25th Oct 11
Submitted 1st Apr 11
Revision Req. 11th Jun 11, Revision recd. 11th Jul & 26th Sep 11
Accepted 28th Sep 11

CASE REPORT

Nephropathic Cystinosis
First reported case in Oman

Dana Al-Nabhani,[1] *Mohammed El-Naggari,[1] Rana Al-Sinawi,[1] Alexander P. Chacko,[1] Anuradha Ganesh,[2] Ibtisam El Nour[1]

الدَّاءُ السِيسْتينِيُّ الكلوي
تسجيل الحالة الأولَى في عُمان

دانا النبهاني، محمد النجاري، رنا السناوي، الكسندر تشاكو، أنورادها غانيش، ابتسام النور

الملخص: يُعد الداء السيستيني الكلوي من الاضطرابات الصبغية الجسدية المتنحية، وهو داءُ الاخْتزانِ في الجُسَيْمَات الحَالَّة التي تتميز بتراكم الحمض الأميني (سيستين) في مختلف الأجهزة والأنسجة. ويمكن أن يظهر الداء على شكل أعراَض كلوية أوغيرها. هناك ثلاثة أنواع من الداء السيستيني ويكون الداء السيستيني الكلوي الوليدي هو الشكل الأكثر شدة. نقدم في هذا التقرير الملامح السريرية المعهودة من الداء السيستيني الكلوي في طفل عُماني. تُعَدّ هذه الحالة نادرة جدا في منطقة الشرق الأوسط، وهي الحالة الاولى التي تم وصفها في عُمان.

مفتاح الكلمات: الداء السيستيني، متلازمة فانكوني، داءُ الاخْتزانِ في الجُسَيْمَات الحالّة، سيستيامن، بلورات، تقرير حالة، عُمان.

ABSTRACT: Cystinosis is an autosomal recessive, lysosomal storage disease characterised by the accumulation of the amino acid cystine in different organs and tissues. It is a multisystemic disease that can present with renal and extra renal manifestations. There are three types of cystinosis, infantile nephropathic cystinosis being the most severe form. In this report we present the classic clinical features of nephropathic cystinosis in an Omani child. This condition remains quite rare in the Middle East and is the first reported case of nephropathic cystinosis in the Omani population.

Keywords: Cystinosis; Fanconi syndrome; Lysosomal storage disease; Cysteamine; Crystals; Case report; Oman.

Cystinosis is a lysosomal storage disease that is inherited in an autosomal recessive manner. Cystinosis, which is a lysosomal transport molecule needed to carry cystine out of the cells, is defective in this disease. This leads to the intracellular accumulation of the amino acid cystine in different organ tissues leading to multiple organ damage with subsequent failure. Infantile cystinosis is the most severe form. Infants appear normal at birth, but soon they fail to thrive and develop renal Fanconi syndrome, due to accumulation of cystine in the proximal tubules. Cystinosis is the most common cause of inherited Fanconi syndrome amongst Caucasians. This condition is frequently reported in the Caucasian population, but has never been reported in Oman. In this report, we describe the first case of infantile nephropathic cystinosis in Oman. Here, we will describe the clinical features, mainly renal and ophthalmological, and include a literature review of cystinosis in the Middle East.

Case Report

A 21 month-old Omani girl was referred to Sultan Qaboos University Hospital for evaluation of severe failure to thrive. This was the second child born to first degree consanguineous parents at full term by spontaneous vaginal delivery. Her birth weight was 2.8 Kg. According to the parents she was doing well until the age of 7 months, when she was noted by the primary care physician to be below the 3rd centile for both weight and height. At that point, it was felt that the failure to thrive was nutritional, since her mother gave history of exclusive breast feeding until the age of 7 months. Despite the nutritional advice and nutritional support for several months, the child did not gain weight and was referred to the Department of Child Health at Sultan Qaboos University Hospital at the age of 21 months with a weight of 5.36 Kgs. The mother gave a history of polyuria, which was suggested by the fact that she had 10 wet diapers per day, polydipsia and

Departments of [1]Child Health and [2]Opthalmology, Sultan Qaboos University Hospital, Muscat, Oman.
**Corresponding Author email: mnaggari@squ.edu.om*

constipation since the age of 18 months. She had a voracious appetite. Developmentally, she was able to sit without support; however, she needed support for standing and walking. She had appropriate social development for her age. The family history was negative for similar conditions and for any renal or metabolic diseases. Also there was no history of miscarriages. On physical examination, the child was dark skinned, identical to her parents' skin complexion. Her growth parameters were as follows: height 66 cm, weight 5.36 Kg, which are both below the 5th percentile; the head circumference was 45.5 cm which was normal for her age. She did not have any dysmorphic features. She had frontal bossing and sparse, thin hair. She also had wide wrists, rachitic rosary, double malleoli and genu valgum. The abdomen was protuberant without organomegaly. The cardiovascular and respiratory examinations were normal. The initial blood investigations are summarised in Table 1. Urinalysis was positive for glucose (+2) and protein (+1) .The urine pH was 5, the specific gravity was 1.010 and the urine anion gap was positive. Urine reducing substances were negative. Urinary amino acid tests were done and showed significant elevation of all measured amino acids with the exception of aspartic acid, methionine, 1-methylhistidine, and turine. An indirect clue of this was the significantly elevated protein to creatinine ratio 106 mg/mmol (normal <50 mg/mmol) with mild proteinuria in the dipstick. The tubular reabsorption of phosphate was 55% (normal > 85%).

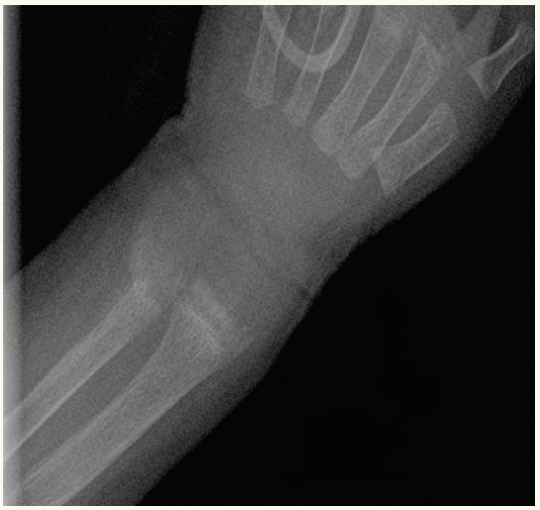

Figure 1: Patient's wrist X-ray showing reduced bone density, widened metaphysis of the ulna and radius with cupping and fraying.

Table 1: Results of the initial blood investigations

Test	Patient result	Reference range
Sodium	132 mmol/L	135–145 mmol/L
Potassium	3.1 mmol/L	3.5–6.1 mmol/L
Chloride	105 mmol/L	98–107 mmol/L
Bicarbonate	17 mmol/L	22–29 mmol/L
Creatinine	16 umol/L	15–31 umol/L
Urea	1.6 mmol/L	2.1–7.1 mmol/L
Anion gap	10 mmol/L	5–13 mmol/L
Total calcium	2.42 mmol/L	2.17–2.55 mmol/L
Corrected Calcium	0.64 mmol/L	2.1–2.55 mmol/L
Phosphate	0.58 mmol/L	1.16–2.10 mmol/L
Alkaline phosphatase	841 units/L	0–281 units/L
Albumin	46 g/L	38–54 g/L
Parathyroid hormone	2.1 pmol/L	1.6–9.3 pmol/L
25-OH Vitamin D	55 nmol/L	22.5– 93.8 nmol/L
1,25 Vitamin D	45 pmol/L	40–140 pmol/L

A wrist X-ray was obtained in view of the physical findings. This showed reduced bone density, widened metaphysis of the ulna and radius with cupping and fraying. No carpal bones were noted and the bone age was delayed [Figure 1]. An abdominal ultrasound was also obtained and this showed normal intra-abdominal organs including two normal kidneys. She also underwent an ophthalmic examination that revealed normal visual acuity in both eyes. No strabismus, nystagmus or ocular motility disturbance was noted. However, slit lamp examination of the anterior segment of both eyes revealed fine, shiny crystal-like deposits diffusely distributed in the corneal epithelium and stroma. The surface of the epithelium was intact and the rest of the examination was unremarkable. The fundus examination showed no abnormal morphology of the disc, macula and vessels and a normal retinal background. With the presence of failure to thrive in a child with renal tubular acidosis and features of Fanconi syndrome, the ophthalmic findings of crystals in the cornea led to the diagnosis of cystinosis [Figure 2]. Retinopathy is usually a late finding of this condition and not seen in early childhood; it is preceded by corneal crystals.

The child was started on supportive treatment

Figure 2: Photo of patient's eye showing crystal deposits in the cornea typical of cystinosis.

which included potassium citrate to correct the metabolic acidosis and hypokalemia, calcium sandoz, phosphate sandoz and alfacaclidol. Calcium was given for the severe hypocalcaemia. Also phosphate supplements were indicated due to severe hypophosphatemia. To avoid the risk of precipitation, a gap of at least four hours was left between each dose of the supplements. With this supportive treatment her weight increased to 7.2 kg and she was able to progress on her motor development milestones. Cysteamine, which is a cystine depleting agent and the mainstay treatment for this disease, had to be ordered since it had never been used before in Oman. She was started on cysteamine 50 mg orally every 6 hrs (30 mg/kg/day) as soon as the medication was available. The aim was to increase the dose slowly to reach 50 mg/kg/day over 4-6 weeks.

Discussion

There are different types of cystinosis: the nephropathic and non-nephropathic. The nephropathic type has renal and extra renal manifestations. This can present in an infantile or late onset form. The infantile form is the most severe and, if left untreated, can lead to end stage renal disease by late childhood. The non-nephropathic type presents with photophobia and only corneal cystine crystals without renal or systemic involvement. This type is also called ocular cystinosis.

Children with the infantile form appear normal at birth. The clinical picture becomes apparent between 3 and 6 months of age. The most common renal manifestation is the renal Fanconi syndrome due to renal proximal tubular dysfunction. This classically presents with failure to thrive, polyuria up to 2–3 litres/day, polydipsia, constipation, dehydration, weakness and hypophosphatemic rickets. Patients will also have glucosuria, proteinuria, phosphaturia, aminoaciduria and metabolic acidosis.

Our patient presented at the age of 7 months with failure to thrive and had the classic features of renal Fanconi syndrome such as polyuria, polydipsia and constipation. She also had signs of rickets clinically, biochemically and radiologically. The laboratory investigations were also classic for renal Fanconi syndrome: normal anion gap, metabolic acidosis with hypokalemia and hypophosphatemia. She also had evidence of renal wasting of glucose which was suggested by normal serum glucose and a positive dipstick for glucose. The protein to creatinine ratio was quite elevated despite normal albumin and minimal proteinuria on dipstick. This suggests that the proteins lost are low molecular weight amino acids rather than the albumin which is a large molecular weight protein. She also had evidence of renal phosphate wasting suggested by hypophosphatemia and low tubular reabsorption of phosphate which was 55% (less than 85% indicates renal wasting).

The other manifestations of nephropathic cystinosis are extrarenal and present later on. These include myopathy and dysphagia due to accumulation of cystine in the muscles, endocrine involvement such as hypothyroidism and diabetes mellitus, hepatomegaly, hypersplenism and photophobia from the corneal accumulation of cystine in the cornea. Fundoscopy may show depigmentaion of the retina. Retinal changes may appear before the corneal features. The corneal crystals require slit lamp examination. These crystals are not present at birth; they appear between 16 and 20 months of age,[1,2] The corneal crystals are virtually pathognomonic. However, their absence does not exclude the diagnosis of cystinosis. Our patient had the typical crystal deposits in the cornea as seen in Figure 2.

Nephropathic cystinosis is the most common cause of renal Fanconi syndrome in the Caucasian population. This disease is quite rare in the Middle East. Only three Middle Eastern countries, Egypt,

Saudi Arabia and Iran, have reported this disease in their populations.[3-5] These studies have provided a lot of important information on nephropathic cystinosis in the region. Soliman *et al.*, in the Egyptian study, were able to identify 16 patients with nephropathic cystinosis out of 33 who presented with Fanconi syndrome to a single centre.[3] The Saudi study, by Aldahmesh *et al.*, identified 8 mutations, 4 of which were novel, in 21 patients with nephropathic cystinosis of Arab origin.[5] The Iranian study by Mirdehghan *et al.* described the clinical features of patients with nephropathic cystinosis presenting over a five year period to a single centre.[4]

The diagnosis of nephropathic cystinosis in this case was based on the presence of corneal cystine crystals in an infant with Fanconi syndrome. Traditionally, white blood cell cystine assay was the test of choice to confirm the diagnosis. This test is not available in Oman and it is costly and technically difficult to perform; there are only a few laboratories worldwide that can perform it. Currently, genetic testing by mutation analysis of the CTNS gene is a better alternative to confirm the diagnosis. It is necessary to consider sending samples to a specialised laboratory in case the diagnosis of nephropathic cystinosis is suspected in an infant younger than 20 months where the cystine crystals might not be present. Early treatment with cysteamine which is a cystine depleting agent can delay the progression to end stage renal disease.

Conclusion

Given the high consanguinity rate in the Omani population, nephropathic cystinosis should be considered in any child presenting with Fanconi syndrome. Immediate referral to a tertiary hospital with nephrology and ophthalmology services is important to avoid delay in treatment.

References

1. Gahl WA, Thoene JG, Schneider JA. Cystinosis. N Engl J Med 2002; 347:111–21.
2. Nesterova G, Gahl W. Nephropathic Cystinosis: Late complications of a multisystemic disease. Pediatr Nephrol 2008; 23:863–78.
3. Soliman NA, El Baroudy R, Rizk A, Bazaraa H, Younan A. Nephropathic cystinosis in children: An overlooked disease. Saudi J Kidney Dis Transpl 2009; 20:436–42.
4. Mirdehghan M, Ahmadzadeh A, Bana-Behbahani M, Motlagh I, Chomali B. Infantil cystinosis. Indian Pediatr 2003; 40:21–4.
5. Aldahmesh MA, Humeidan A, Almojalli HA, Khan AO, Rajab M, Al-Abbad AA, et al. Characterization of CTNS mutations in Arab patients with cystinosis. Ophthalmic Genet 2009; 30:185–9.