Case Report

A case report of a rare cause of hypophosphatemic rickets-cystinosis

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Abstract

Background: Bowed legs and failure to thrive in children must be thoroughly investigated.

Rickets results from deficient mineralization at the growth plate and can lead to bone deformation. The leading cause is vitamin D deficiency, but in rare cases, rickets can be caused by abnormalities of phospho-calcic metabolism, either primary (inherited) or secondary.

Case: A two-year-old boy presented with bowed legs and failure to thrive.

Investigations revealed hypophosphatemic rickets from renal Fanconi syndrome due to infantile cystinosis.

The patient was then treated with oral cysteamine and electrolytes, and the genu varum slowly improved.

Conclusion: Cystinosis is a rare disease with multiple presentations but should not be overlooked when diagnosing hypophosphatemic rickets.

Introduction

Rickets is caused by deficient mineralization at the growth plate and ultimately can lead to bone deformation. It is mainly caused by vitamin D deficiency, but in rare cases, can also be caused by abnormalities of phospho-calcic metabolism, either primary (inherited) or secondary. This may be due to low calcium or phosphorus intake, poor mineral absorption, or excessive mineral excretion. Loss of phosphorus leads to hypophosphatemia, inhibiting caspase-9-mediated mitochondrial pathways and chondrocyte apoptosis and leading to growth-plate hypertrophy, osteoid accumulation, decreased strength, and stability bow-legs (1). Analysis of phosphocalcic blood balance and wrist and knee X-rays are recommended to confirm Rickets diagnosis.

In the case of elevated PTH (parathormone) with typical to low calcium and phosphorus levels, 'the missing calcium' leads to 'calcipenic rickets,' in which vitamin D metabolism should be investigated. On average, with slightly elevated PTH with low phosphorus and normal calcium levels, lack of phosphorus leads to hypophosphatemic rickets (Table 1), and urine analysis should check phosphorus loss (2,3).

Fibroblast growth factor-23 (FGF-23), produced by osteocytes and osteoblasts, is the principal phosphate regulating hormone.

FGF-23 is elevated in a few HR phenotypes, decreasing phosphate reabsorption by downregulating sodium phosphate cotransporters in the proximal tubules, resulting in phosphaturia and hypophosphatemia (4).

Table 1. *Hypophosphatemic rickets (HR): steps to diagnosis.*

<table>
<tr><td colspan="4">Serum PTH normal or low</td></tr>
<tr><td>Low urine phosphorus</td><td colspan="3">High urine phosphorus</td></tr>
<tr><td rowspan="3">· Insufficient phosphate intake
· Decreased gastrointestinal absorption
· Internal re-distribution
· Dialysis</td><td colspan="2">Normal or low serum FGF-23</td><td>High serum FGF-23</td></tr>
<tr><td>Excessive loss of amino acids, bicarbonate, and glucose in urine</td><td>Excessive loss of calcium in urine</td><td rowspan="2">· Hereditary HR
- X-linked recessive HR (PHEX gene)
- Autosomal dominant HR
- Autosomal recessive HR
· Acquired HR</td></tr>
<tr><td>Fanconi Syndrome
· Acquired causes (drug, heavy metals)
· Hereditary causes
- Cystinosis (autosomal recessive)
- Inborn errors of metabolism
- Dent disease
- …</td><td>Hereditary HR with hypercalciuria (autosomal recessive)</td></tr>
</table>

Hypophosphatemic rickets (HR) has many aetiologies: low phosphorus intake, urinary phosphate losses from proximal tubulopathy (renal Fanconi syndrome), or hypophosphatemia linked to fibroblast growth factor-23 (FGF-23).

Renal Fanconi syndrome can be inherited (cystinosis is the most common cause) or acquired (from drugs, heavy metals, chemotherapy) (Table 1).

Infantile cystinosis is a rare autosomal recessive condition caused by mutations in the *CTNS* gene, which causes a deficiency in cystinosin, a lysosomal proton-activated cystine transporter, with an incidence of 1 in 100,000 to 200,000. Cystine accumulates in lysosomes throughout the body, damaging cells and causing organ problems. Cystinosis is the most common hereditary cause of renal Fanconi syndrome, involving generalized proximal tubular dysfunction (5).

Rickets is caused by urine loss of phosphorus leading to hypophosphatemia. Clinical diagnosis of infantile cystinosis is based on symptoms such as is vomiting and failure to thrive.

We report an unusual clinical presentation of Rickets in a two-year-old child.

Case report

We report the case of a two-year-old boy with bowed legs and no medical history. He started irregularly walking at 13 months and had previously (during the first six months) received oral vitamin D supplementation.

Parents hadn't observed any signs of polydipsia or polyuria, though mild polydipsia was noticed after a thorough anamnesis.

Clinical findings

The growth charts (Figure 1) showed failure to thrive (height: 73.5 cm (-4,8 SD); weight: 10 kg (-2,6 SD), BMI 18,5 kg/m^2 (1,9 SD)).

Overall, the physical exam was routine, except for bowed legs and red eyes (diffuse redness of the sclera).

Diagnostic Assessment

An orthopedic surgeon was consulted initially for bowed legs. X-ray (Figure 2A) revealed severe bilateral genu varum suggesting rickets, and the patient was then referred to a rheumatologist.

Blood analysis (all values available in Table 2) revealed renal insufficiency (eGFR Schwartz equation, 60 ml/min/1.73 m^2), hypophosphatemia, hyperchloremic acidosis, and low 25-hydroxyvitamin D. Thyroid hormones (TSH and T4 free), insulin-like growth factor-1, 1,25-hydroxyvitamin D and 1,84-parathyroid hormone were normal.

Normal PTH allowed us to exclude the hypothesis of calcipenic rickets. Alkaline phosphatases and C-terminal collagen crosslinks were elevated, suggesting an osteolytic process. Therefore, the patient was diagnosed with hypophosphatemic rickets. Proximal tubular acidosis related to renal Fanconi syndrome was diagnosed according to blood and urine results (all values available in Table 2), showing metabolic acidosis associated with urine losses: proteinuria (mixed proteinuria of nephrotic range), phosphaturia (according to TRP and TMP/GFR values), calciuria, natriuria, glycosuria, amino-aciduria and loss of bicarbonate. Alkaline urine in blood acidosis is suggestive of tubulopathy.

No history of medication or heavy metal exposure was reported. Renal ultrasonography showed accentuation of cortico-medullar differentiation and absence of established nephrocalcinosis; however spotty echogenic pyramids could have been caused by tubular deposits. Ophthalmologic examination revealed corneal cystine crystals, pathognomonic for cystinosis, thus establishing the diagnosis (Figure 2B).

The diagnosis was further confirmed by high levels of cystine found in WBCs three months after the first visit. Genetic analysis revealed two heterozygous mutations in the *CTNS* gene: a 65kb deletion and a nonsense mutation: c.978G>A – p.Trp326*.

Therapy

Treatment with 25-OH-vitamin D, alphacalcidol (0.04 µg/kg/day), and phosphorus with anhydrous phosphate solution (1 mmol/kg/day) were initiated.

Symptomatic treatment with sodium supplements, potassium bicarbonate, and carnitine was added later. Specific treatment with oral mercaptamine

Figure 1 : *Growth charts.*
Initiation of symptomatic followed by specific mercaptamine (cysteamine) treatment at 30 months of age. Persistence of short stature.

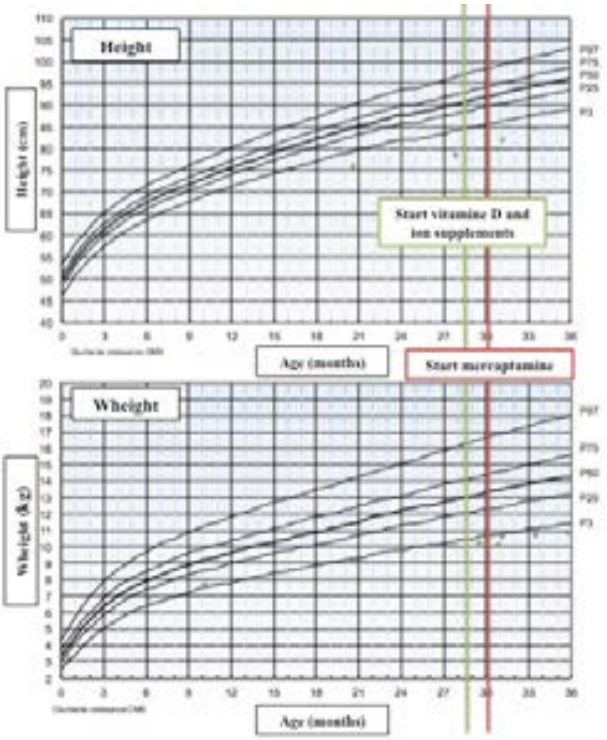

Figure 2 : *Imaging results.*
(A) X-ray of the front of right leg showing irregularities on femoral and tibial metaphyseal plates suggesting rickets. (B) Slit-lamp image revealing corneal cystine crystals pathognomonic for cystinosis.

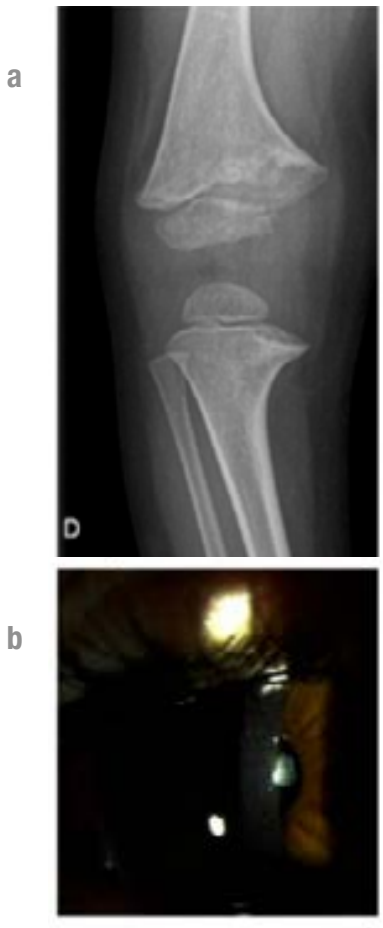

Table 2. *Analyses*

Analysis	Results	Norms	Units
Biology (month 0)			
Bicarbonate	16	(20 - 28)	mmol/L
Chlorine	110	(98 - 107)	mmol/L
Calcium	2.49	(2.20 - 2.70)	mmol/L
Phosphorus	1.04	(1.29 - 2.20)	mmol/L
Urea	24	(11 - 36)	mg/dl
Creatinine	0.54	(0.24 - 0.41)	mg/dl
Alkaline phosphatase	526	(156 - 369)	U/L
25-hydroxy vitamin D	20.3	(20 - 25)	ng/mg
1,25 $(OH)_2$ vitamin D	86	(25 - 86)	pg/ml
1,84-parathyroid hormone	24.1	(4.6 - 38.4)	ng/L
Carboxy-terminal collagen crosslinks	1140	(16 - 584)	pg/ml
Urinalyses (month 0)			
TRP	55	> 80	%
TMP/GFR	0.575	1.15 – 2.44	
Calcium U/ creatinine U	1.44	0.5 = P95	mg/mg of creatinine
Proteins/creatinine	3	< 0.2	g/g
Biology (Month 3)			
Bicarbonate	16	(20 - 28)	mmol/L
Anion gap	14	(8 – 16)	mmol/L
Carnitine	11.06	(23.9-51.9)	µmol/L
Intra-leucocyte cystine	7.17	< 0.4	nmol of 1-2 cystine per mg of protein
Urinalysis (month 3)			
pH	7.0		
Urinary anion gap	77.9		mmol/L
Glucose	5.2	< 0.15	g/L
Fractional excretion of sodium	1.5%		
Beta 2-microglobulin	120	< 0.2	mg/L
Microalbuminuria	886.2	< 30	mg/g of creatinine

(cysteamine), bitartrate, and mercaptamine chlorhydrate eye drops was started soon after diagnosis (at 30 months). Cysteamine at a starting dose of 10 mg/kg/day (0.2 g/m²/day) was increased over five weeks to 56 mg/kg/day (1.2 g/m²/day).

The patient then developed moderate polyuria, treated with indomethacin to minimize renal fluid and electrolyte losses.

Outcomes

After nine months of treatment for phosphorus deficiency, leg straightening and improved walking was observed with the resumption of growth but the persistence of short stature (height: 85,5 cm (-3,1 SD) and stable weight charts (11 kg (-3 SD)) (BMI overall thus decreasing to 15 kg/m² (-0,6 SD)).

Renal insufficiency was improved: The Schwartz value increased to 75 ml/min/1.73m$^{2.}$ corresponding to CKD2. Leucocyte cystine levels remained high, 2.95 and 6.5 nmol/1/2 cystine/mg protein, so cysteamine was increased to 73 mg/kg/day (1,6 g/m²/day). Mild photophobia appeared despite eye drops.

However, one year after establishing the diagnosis, compliance issues popped up.

To address these issues, a pediatric nephrology agreement provided free access to paramedical consultations (therapeutic education nurse, dietician, and psychologist). The social worker provides assistance to the family.

Discussion

Infantile cystinosis (autosomal recessive disease) is caused by mutations in the *CTNS* gene (17p13.2), which codes for cystinosin, a lysosomal cystine-proton cotransporter. Cystinosin deficiency is associated with elevated cystine levels in lysosomes, defective endo-lysosomal trafficking, mitochondrial impairment, increase in ROS and apoptosis, and autophagy changes (6). Deficiency leads to the accumulation of cystine in all organs (6).

Fanconi syndrome is characterized by urine excretion of amino acids, glucose, bicarbonate, sodium, potassium, and phosphorus due to atrophy and death of cystinotic proximal tubular cells (6). Glomerular cells are progressively affected, inducing proteinuria. The end-stage renal disease occurs around ten years of age if untreated (6).

Extra-renal manifestations can also occur, causing ophthalmological, endocrine (thyroid), and neuromuscular issues (muscular weakness, swallowing issues…), etc. (7).

The accumulation of cystine crystals in the eyes can progressively lead to photophobia (related to the density of crystals, infiltration, inflammatory cells, and nerve damage within the cornea), blepharospasm, keratopathy, and corneal erosions (8).

Infantile cystinosis is a rare cause of hypophosphatemic rickets but the most frequent hereditary cause of renal Fanconi syndrome (5).

Renal Fanconi syndrome in infancy results in HR from hypophosphatemia, metabolic acidosis, 1,25-vitamin D deficiency, and hypocalcemia (9).

Patients with nephropathic cystinosis suffer from the cystinotic metabolic bone disease (CMBD), leading to HR and renal osteodystrophy. CMBD can cause osteomalacia, osteoporosis, bone deformation, short stature, and, more frequently, bone fractures. Uncorrected acidosis worsens bone damage and urinary calcium loss (9). Florenzano et al. discovered that rickets or osteomalacia from nephropathic cystinosis was responsible for 64% of the long bone deformities. The mean age of patients was 20 years old (5).

Contrary to this young patient, other reported cases of bone deformities occurred in older patients, with the initial presentation lacking bowed legs. (10, 11).

Early diagnosis of cystinosis relies on clinical information, urinalysis, and ocular slit-lamp examination. If the ophthalmologist confirms corneal crystals, a diagnosis of cystinosis should be made. Treatment should be started without molecular confirmation, considering corneal crystals could be absent in a very young patient.

After diagnosis, our patient received specific treatment with cysteamine. Oral cysteamine decreases glomerular renal function decline but has no direct effect on proximal tubulopathy or Fanconi syndrome (9). Phosphorus and bicarbonate supplementation minimize CMBD. Oral cysteamine delays renal failure and postpones metabolic bone disease due to CKD. Cysteamine eye drops are necessary because oral cysteamine does not reach the cornea, lacking a vascular system.

We observed a reduction in the redness of the sclera.

Treatment compliance was, however, poor, possibly because of polypharmacy.

The late diagnosis and concurrent late start of treatment partly explain our patient's chronic renal failure and bow legs. Electrolyte supplementation (phosphorus and bicarbonate) corrects the genu varum and prevents HR from getting worse.

When treatment is initiated before one year with correct compliance, end-stage renal disease in adulthood can be avoided. Therapeutic compliance remains difficult, however.

As shown in this case of a well-proportioned child, BMI is not enough. To monitor failure to thrive, every child should maintain growth charts.

Nutrition scores, such as the Waterlow score, were not used in this case, as small height related to cystinosis could have led to misinterpretation.

If failure to thrive and, in detail, short stature had been diagnosed and investigated earlier, Fanconi syndrome and cystinosis could have been diagnosed earlier, avoiding the appearance of rickets.

Conclusions

We present a case of Rickets with an unusual appearance. Bowed legs, red eyes, and failure to thrive are all clinical signs that should be thoroughly investigated. Urinary dipstick, spot, and blood tests should rule out renal Fanconi syndrome. Cystinosis is one of the most common causes of hypophosphatemic rickets and the most common cause of inherited renal Fanconi syndrome. Early diagnosis, treatment, and care require multidisciplinary collaboration, partly because targeted early therapy improves prognosis.

Conflict of interest

The authors have no conflict of interest to declare.

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