CLINICAL VIGNETTE

Fanconi Syndrome, Metabolic Bone Disease and Growth Retardation in the Child

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Introduction

Cystinosis is a rare genetic disorder characterized by the accumulation of cystine within cells. This autosomal recessive condition is caused by a mutation in the *CTNS* gene, which codes for cystinosin, a lysosomal cystine transporter. This mutation affects the transport of cystine out of lysosomes and results in cystine buildup in various organs and tissues, manifesting typically in childhood.[1] The kidneys and eyes are especially vulnerable to damage from this build-up. The muscles, thyroid, pancreas, and testes may also be affected.[2]

One of the most common manifestations of cystinosis is renal Fanconi syndrome, a type of renal disease that causes certain molecules such as phosphorus, to be eliminated in the urine rather than being absorbed into the bloodstream.[2] The loss of minerals, salts, fluids, and other nutrients has the potential to impair growth, as can be seen with hypophosphatemic rickets, where bones are soft and 'bowed.' Nutrient imbalances also lead to increased urination, thirst, dehydration, and hypochloremic metabolic acidosis.[3]

Children diagnosed with cystinosis often suffer from growth retardation due to a combination of factors. In addition to nutritional deprivation due to renal Fanconi syndrome, children can develop chronic kidney disease (CKD), feeding difficulties often requiring tube feeds and accumulation of cysteine in the bone which can all contribute to growth retardation. Patients who have nephropathic cystinosis can also suffer from cystinosis-related metabolic bone disease (CMBD), which manifests as hypophosphatemic rickets in infancy, renal osteodystrophy, bone deformities, osteomalacia, osteoporosis, fractures, and short stature.[4]

Renal transplantation is curative of renal disease and may reverse growth deficiency. Our case is young child with cystinosis and CMBD, supported by longitudinal bone growth studies, who received a renal transplant with early evidence of reversed growth deficiency.

Case

The patient is a young female diagnosed with cystinosis and Fanconi syndrome. She has been under the care of multiple medical specialties in our institution since infancy, including nephrology, endocrinology, gastroenterology, ophthalmology, and nutrition. The patient takes several nutritional supplements, including iron, sodium bicarbonate, Phos-Na/K packages, Vitamin D, levocarnitine, potassium citrate, and procysbi, or cysteamine-bitartrate, a cysteamine-depleting agent. The patient receives these supplements through a gastrostomy feeding tube which undergoes exchange approximately every 3 months. Despite her treatment, the patient experiences recurrent and refractory abdominal distension, fullness, and non-biliary emesis. These symptoms have been partially managed with cyproheptadine and metoclopramide, which have increased her ability to tolerate oral intake.

At the age of 4, the patient was started on growth hormone injections to address her short stature. However, despite various adjustments to her dosage, her bone age studies have consistently shown a delay in bone growth compared to her chronological age. At the chronological age of 8 years and 5 months, the patient's bone age was between 5 years 9 months and 6 years 10 months, placing her in the 0.9th percentile for bone age by the method of Greulich and Pyle[5,6] (Figure 1a). At the age of 9 years 9 months, the patient's bone age was six years ten months (Figure 1b) and at 11 years 4 months, her bone age was 8 years 41 months. Soon after the patient received a renal transplant, further bone studies were obtained. At 12 years 3 months, her bone age was 10 years, and at 13 years 1 month, her bone age was 11 years (Figure 1c).

As with most Cystinosis cases, this patient was also monitored since infancy for kidney function and the development of chronic kidney disease (CKD). Renal ultrasound demonstrated smaller-than-expected kidneys compatible with CKD, but without hydronephrosis or discrete masses (Figure 2). She was placed on lisinopril to manage her chronic kidney disease however her renal function continued to deteriorate with a baseline creatinine of 2.5 mg/dL and BUN between 24-51 mg/dL. At the age of 12 years 3 months, she received a live donor kidney transplant from her mother. Post operatively, she was placed on prednisone and immune suppressant therapy, including everolimus and tacrolimus. One week after starting everolimus, the patient developed abdominal pain with bright blood per rectum. Colonoscopy revealed ulcers and biopsy was compatible with drug-induced colitis. Everolimus was discontinued and prednisone was increased to 10mg daily. The patient's abdominal symptoms subsided and her prednisone was decreased to 4mg daily. After her kidney transplant, her growth hormone treatment was discontinued and she was found to have excellent interval height velocity, growing slightly faster than her normal pubertal rate and demonstrating catch-up

growth (Figure 3). Her creatinine levels stabilized to 0.6 mg/dL and her BUN levels to 13-20 mg/dL.

Diagnosis and Management

Based on the patient's clinical presentation and laboratory findings, cystinosis and Fanconi syndrome were confirmed. The management of cystinosis involves medications to remove excess cystine and prevent kidney damage, as well as dietary restrictions. The patient is currently taking *procysbi*, a cystine-depleting agent, as well as other medications and nutritional supplements to support her nutritional status. Cystine depletion is based on reducing cystine to allow it to exit lysosomes, bypassing the biochemical deficit of the disease.[7,8] In a study of 100 Cystinosis patients on cystine depletion therapy, the frequency of diabetes mellitus, myopathy, pulmonary dysfunction, hypothyroidism all decreased as time on cysteine therapy increased.[9]

In our patient, growth hormone therapy was initiated to address the patient's growth delay and was adjusted per the patient's tolerance and treatment results. Ultimately, a renal transplant from her mother contributed to normalizing renal function resulting in improved bone growth and catch up growth. Growth hormone therapy has since been discontinued.

Discussion

Cystinosis is a rare genetic disorder that affects cystine transport within cells, leading to the cysteine crystal accumulation and visceral organ damage. Early diagnosis and treatment are essential for managing the condition including medical management and dietary modifications. Corneal cystine accumulation can be appreciated as early as 12 months by slit lamp examination.[3,8] Our patient had been prescribed lubricating eye drops which served as a prophylactic treatment for potential photophobia and blepharospasm.

Growth hormone (GH) deficiency is a common complication of cystinosis and can result in stunted growth. The role of growth hormone in the treatment of cystinosis is supported in the literature, especially in the absence of adequate cystine-depleting treatment initiated early in infancy.[8] It is unknown exactly when the patient began her cystine-depletion treatment, but she had already been prescribed the medication from our earliest history at four years old. It is impossible to determine the significance of this treatment on her current height and weight, but the fact that she remained below -2 standard deviations at nine years and nine months may indicate that she had not responded adequately to the treatment. In Besouw et al., 25% of patients did not respond to GH and remained below 4 standard deviations of height.[10]

The renal manifestations of cystinosis include cystinosis metabolic bone disease (CMBD), leading to hypophosphatemic rickets, delayed bone growth and constitutional short stature. In a study of 49 children with nephropathic cystinosis (NC) and 80 CKD controls of the same age and CKD stage, patients with NC show more severe skeletal comorbidity associated with distinct CKD stage-dependent alterations of bone metabolism, which was only partially normalized after renal transplantation.[4] This patient's delayed growth has been well documented, both by several bone wrist studies (Figure 1) and the child's height and weight (Figure 3). When the patient received her renal transplant, her renal function immediately corrected as expected, in addition to a moderate correction of her delayed growth, despite discontinuation of her growth hormone therapy. At the time of writing this case report, it has been approximately 1 year since her transplant, and more time is needed to appreciate further growth correction. Per the recommendations of a 2016 international conference on the treatment of Cystinosis, GH may be re-started in case of persistent short stature (>12 months after transplantation).[4]

Conclusion

Cystinosis is a rare genetic disorder that affects cystine transport within cells and can cause kidney failure and other symptoms such as malnutrition, growth delays, and vision problems. Early diagnosis and treatment, especially cystine-depleting strategies, are essential for managing the condition. Growth hormone therapy effectively improves linear growth in children with cystinosis, but other factors, such as malnutrition or kidney disease, may also contribute to growth delay. Renal transplant is curative of the Cystinosis related CKD and has been shown to reverse growth delays.

Figures

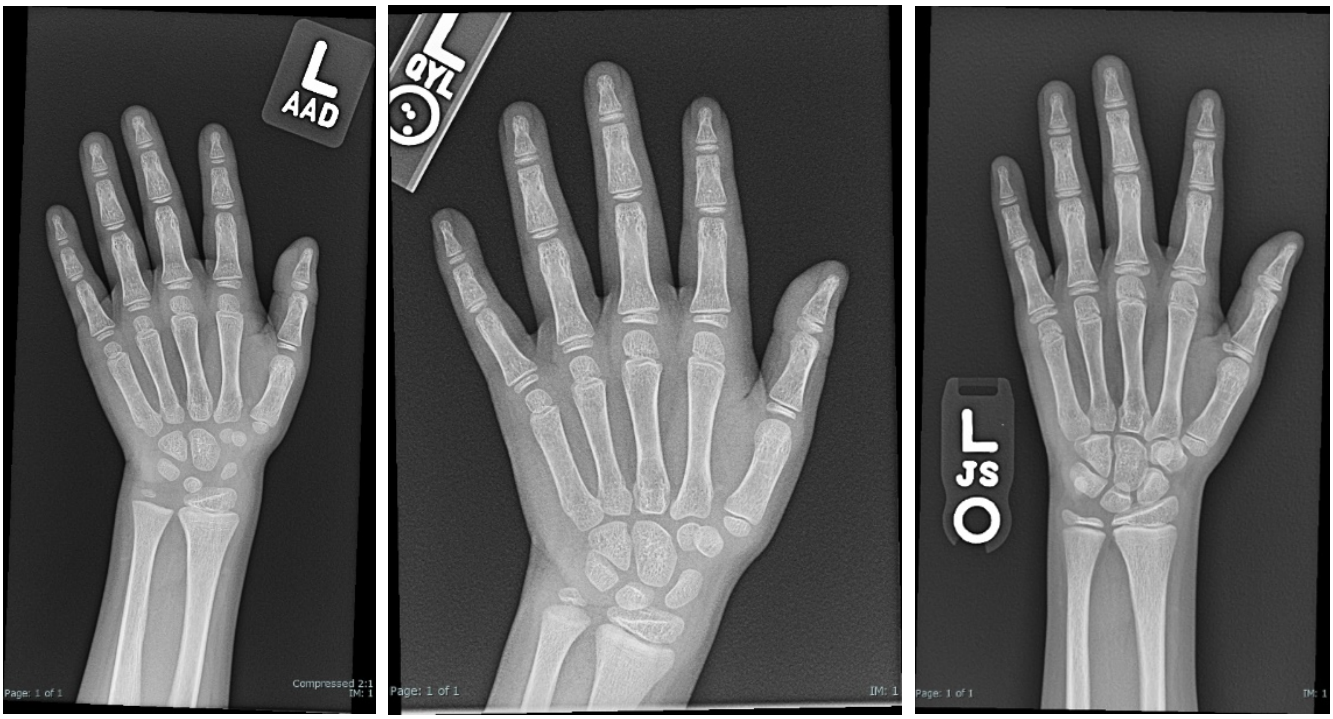

Figure 1. Wrist XR studies at patient with cystinosis-related metabolic bone disease (CMBD) at ages of (a) 6 years and 10 months, (b) 9 years and 9 months, and (c)12 years and 3 months.

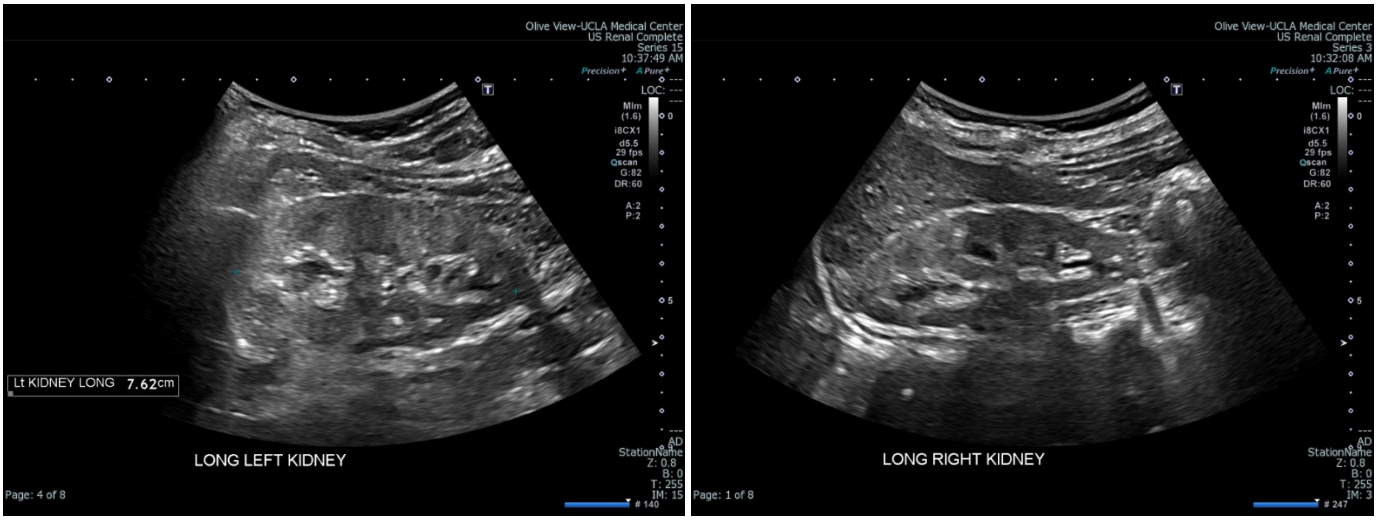

Figure 2. Renal US demonstrating small kidneys without evidence of hydronephrosis or discrete masses, shown in the long axis of the (a) left kidney and (b) the right kidney.

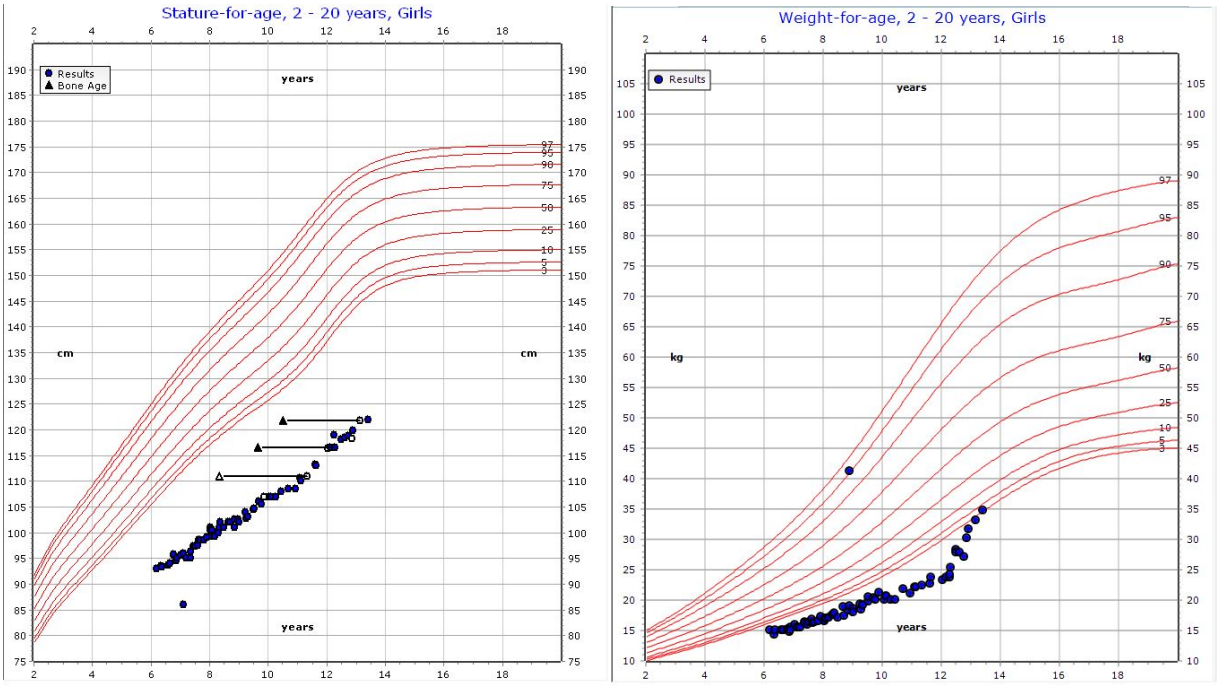

Figure 3 Growth charts demonstrating the patient's (a) stature in centimeters and (b) weight in kilograms. Red curves demonstrate normal percentiles, denotes by the number to the right of the curve, for the average stature and weight for girls aged 2 to 20 years. The patient's measured values from the EMR are denoted by blue circles, while the measured bone ages are denoted by triangles in the stature chart. Note that one value measured under weight between the patient's age 9 to 10 was incorrectly charted (likely input as pounds instead of kilograms).

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