Brief Communication

Refractory rickets due to Fanconi's Syndrome secondary to Wilson's disease

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ABSTRACT

Renal tubular disorders are an important cause of refractory rickets. Wilson's disease, an inherited disorder of copper metabolism has varied presentations. We present a case of refractory rickets due to Fanconi's syndrome attributable to Wilson's disease. An adolescent girl presented with pain in the hip and knee joints and a knock-knee deformity since six years. She had received multiple doses of cholecalciferol with little improvement. There was no history of seizures, polyuria, jaundice, intake of drugs, or similar complaints in the family. Examination revealed a severely short stature with widening of the wrist joint and genu valgum. Examination of the central nervous system (CNS) was normal. Skeletal radiographs showed features suggestive of rickets at the hip and knee joints. Routine biochemistry was normal, 25-hydroxyvitamin D [25(OH)D] was adequate (57.1 ng/dL), with normal corrected calcium (9.24 mg/dL), low phosphate (2.76 mg/dL), elevated bone-specific alkaline phosphatase, and normal renal functions. Twenty-four-hour urine revealed phosphaturia, kaliuresis, and glucosuria with normal blood sugars and aminoaciduria. Blood gas analysis revealed normal anion gap metabolic acidosis with a urine pH of 7. Ammonium chloride (NH_4CL) challenge test revealed proximal tubular acidosis. A search for causes revealed Kayser-Fleischer rings. The diagnosis of Wilson's disease was confirmed by low serum ceruloplasmin levels (6.5 mg/dL; normal: 18–35 mg/dL) with high 24-hour urine copper levels (433 mcg; normal: 20–50 mcg). She was started on a replacement of alkali, phosphate, calcium, and vitamin D, with zinc acetate for Wilson's disease. Rickets as a presenting feature of Wilson's disease has been reported rarely. Recognition of this entity is important, as treatment of the primary condition may improve tubular function as well.

Key words: Fanconi's syndrome, refractory rickets, Wilson's disease

Introduction

The most common cause of rickets in children is deficiency of vitamin D and it responds well to replacement. In patients who are refractory to a replacement of vitamin D, a detailed search for other etiologies of rickets like hypophosphatemic rickets including renal tubular acidosis, renal osteodystrophy, and vitamin D-resistant rickets is warranted.[1] Proximal renal tubular acidosis when accompanied by other proximal tubular defects like glucosuria, aminoaciduria, uricosuria, and phosphaturia is referred to as Fanconi's syndrome[2] and is a rare but important cause of short stature and hypophosphatemic rickets. Fanconi's syndrome can either be a primary abnormality in the renal tubular cells or secondary to prerenal disorders in which toxic metabolic substances lead to the derangement of tubular functions like cystinosis, Wilson's disease, tyrosinemia, galactosemia, and Lowe's syndrome.[2]

Wilson's disease is an inherited disease involving a defect of copper transport by the hepatic lysosomes which leads to excess deposition of copper in the organs, with hepatic and neuropsychiatric manifestations being the presenting feature.[3] Rickets as the presenting feature of Wilson's disease has been reported very rarely.[4]

We present a child of 13 years presenting with rickets refractory to replacement of vitamin D due to Fanconi's syndrome secondary to Wilson's disease.

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Case Report

A 13-year-old girl, first-born of a nonconsanguineous marriage, with normal perinatal history and developmental milestones, presented with complaints of an insidious onset of progressive weakness involving both lower limbs, in the form of a difficulty in getting up from a squatting position since six years. She also noticed pain in her hips and lower limbs with a gradual development of knock-knees over the same period of time. She had pain and discomfort in her elbow and knees joints. Her dietary intake included about 450 mL of milk per day. Sun exposure was adequate. She had received multiple cycles of vitamin D sachets over the six-year period with minimal improvement. There was no history of tingling around the mouth or the fingertips and no history of polyuria, swelling of lower limbs, jaundice, persistent diarrhea, or intake of drugs. There was also no history of similar complaints among the family members.

Examination revealed an oriented, alert, poorly built, poorly nourished child (weight: 18.6 kg, <3rd percentile) with a severely short stature [height: 120 cm <3rd percentile, standard deviation score (SDS): -5.43, target height: 146 cm, SDS: -2.48], mildly pale, nonicteric, and stable vitals. Examination of musculoskeletal system revealed widening and tenderness of wrists with valgus deformity at knees [Figure 1]. Examination of the central nervous system revealed normal mental functions, cranial nerve, and sensory system. Examination of the motor system showed normal tone and a power of 4/5 in the muscle groups in all the limbs with normal reflexes. The patient also had a palpable liver with a span of 11 cm, and no nodularity or tenderness. No palpable spleen or shifting dullness was noted.

Biochemical evaluation revealed mild microcytic hypochromic anemia, normal renal functions, normal transaminases, low albumin, hypokalemia, elevated bone-specific alkaline phosphatase, normal corrected calcium, hypophospatemia, and adequate levels of 25-hydroxyvitamin D [Table 1]. Twenty-four-hour urine levels of phosphate and creatinine were 0.29 g and 277 mg, respectively. Tubular maximum reabsorption of phosphate per unit of glomerular filtrate (TmP/GFR) was low at 1.4 mg/dL, indicating a renal loss of phosphate. Arterial blood gas analysis revealed normal anion gap metabolic acidosis with a urine pH of 7. Skeletal radiography revealed epiphyseal dysgenesis with a loss of horizontal trabeculations at both femoral necks, pseudofractures around the knees, and widening of epiphysis of both knees and wrists [Figure 2]. Ammonium chloride challenge test done to check the ability to acidify urine was positive, suggesting proximal tubular dysfunction [Table 2]. On further testing, she was found to have glucosuria in the presence of normal blood sugars and also aminoaciduria, thus suggesting a diagnosis of Fanconi's syndrome. To screen for causes of Fanconi's syndrome, a slit-lamp examination was done and it revealed the presence of Kayser-Fleischer rings which prompted an evaluation for Wilson's disease [Figure 3]. Serum ceruloplasmin levels were low and 24-hour urine copper levels were high [Table 1]. A detailed examination of the central nervous system revealed spastic dysarthria. Ultrasonography of the abdomen showed

Table 1: Investigations

Corrected calcium (mg/dL)	9.24 mg/dL
Serum phosphate	2.76 mg/dL
Alkaline phosphatase	1245 U/L , >80% bone origin
25-hydroxyvitamin D	57.2 ng/dL
Creatinine	0.55 mg/dL
Potassium	2.72 mEq/L
Urine routine	Ph 7, sugar and amino acid present
Serum ceruloplasmin	6.5 mg/dL (18–35 mg/dL)
24-hour urine phosphate	0.29 g/24 hours
24-hour urine creatinine	277 mg/24 hours
24-hour urine copper (20–50)	433 mcg/24 hours

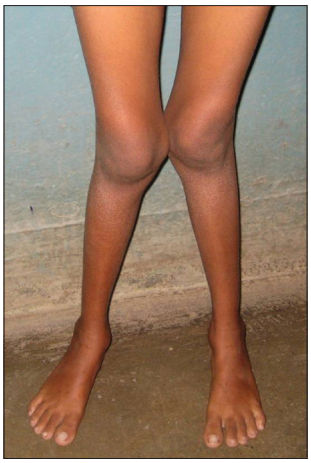

Figure 1: Photograph of lower limbs of the child showing genu valgum deformity (knock-knees)

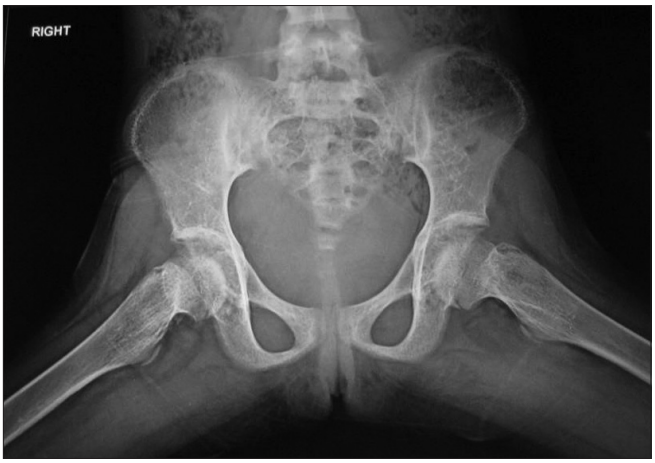

Figure 2: Radiograph of hip joint showing femoral epiphyseal dysgenesis and loss of horizontal trabeculations suggestive of rickets

Table 2: Ammonium chloride challenge test (0.1 g/kg body weight)

Time	urine pH	blood pH	Serum HCO_3^-
Basal	7	7.36	21 meq/L
1 hour	5.74		
2 hours	5.58		
3 hours	5.42	7.22	14 meq/L
4 hours	5.07		

HCO_3^-: Hydrogen carbonate

a normal-sized liver with coarse architecture; portal vein, spleen, and kidneys were normal. Prothrombin time and upper gastrointestinal endoscopy were normal. Magnetic resonance (MR) imaging of the brain showed bilateral symmetrical hyperintensities in T_2-weighted images in the basal ganglia, midbrain, periaqueductal areas, cerebellum, and the frontal lobes consistent with Wilson's disease. Thus a diagnosis of short stature and refractory rickets due to Fanconi's syndrome secondary to Wilson's disease was made. She was started on a replacement of potassium and alkali in the form of potassium Shohl's solution 20 mL thrice a day (t.i.d) and replacement of phosphate with Joule's solution along with a replacement of calcium and vitamin D. Wilson's disease was treated with zinc acetate tablets 50 mg three times a day.

Discussion

Though the majority of rickets is due to deficiency of Vitamin D, it is important to be vigilant of the cases which do not respond adequately to its replacement. In a review of refractory rickets in nonazotemic Indian patients, renal tubular diseases accounted for about a third of the cases.[5] Rickets and osteomalacia are more common in Fanconi's syndrome as compared to other renal tubular diseases.[2] Wilson's disease, though its exact prevalence is not known in our country, is believed to be under-reported and may have a slightly varied clinical profile in terms of presentations

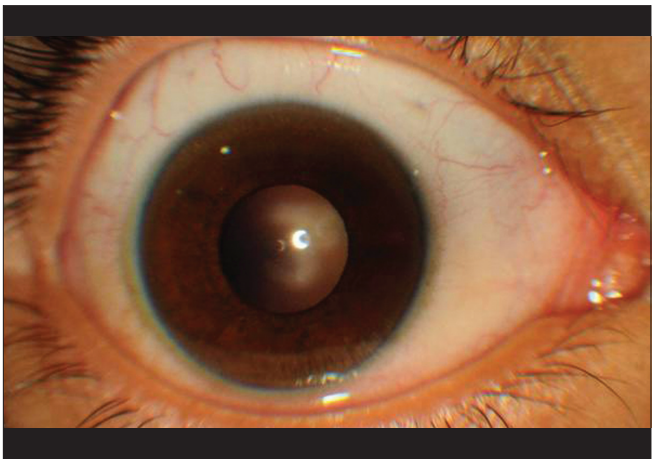

Figure 3: Photograph of Kayser-Fleischer rings

in the first or second decade, and the musculosketetal form is more common.[3] The importance of making an etiological diagnosis in Fanconi's syndrome is important in that Wilson's disease is one of the few conditions which, on treatment, may improve tubular function over time.

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