Primary Fanconi Syndrome

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The Fanconi Syndrome is a generalized proximal tubule defect leading to urinary wasting of many solutes such as glucose, amino-acids, phosphates and bicarbonates that results in polyuria, growth failure and resistant rickets(l,2). It is an. uncommon tubulopathy and is usually secondary to a systemic disease, metabolic disorder or drug toxicity. Of the 40 inherited tubulopathies seen at our nephrology clinic, there have been only 6 cases of Fanconi Syndrome, 5 of which were secondary. Primary Fanconi Syndrome is quite rare and has not been reported earlier in Indian literature.

Case Report

A 4 year old Muslim girl presented with inability to walk, repeated respiratory tract infections and failure to thrive. She was the second child of a non-consanguinous marriage and had a normal 6 year old sister. She was born of a full term normal delivery with a birth weight of 2.5 kg and failed to thrive despite a normal dietary intake. Her physical milestones were delayed but she was mentally normal. She had no history of vomiting, jaundice, convulsions or photophobia. The child had received 2 doses of vitamin D orally prior to her admission to our hospital.

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On examination, her weight was 7.5 kg and length 76 cm (<5th percentile for age). She had an open anterior fontanelle, frontoparietal bossing, a bell shaped chest with beading of the ribs, Harrison's sulcus, flaring of the bones at the wrists, double malleoli and bowing of the lower limbs. She had no cataracts, icterus or pallor. Her abdomen was distended and a soft to firm liver was palpable 3 cm below the costal margin. The spleen was not palpable. There were bilateral rales in her chest. She had marked hypotonia with normal power and reflexes. Her fundus was normal.

Investigations revealed a negative mantoux test, Hb-11.4 g/dl, blood urea nitrogen -8 mg/dl (N 8-23), serum creatinine 0.1 mg/dl (N 0.6-1.5), serum - albumin 3.8 g/dl (N 3.5-6.0), serum cholesterol 160 mg/dl (N 150-250), serum calcium 6.8 mg/dl (N 8.8-11), serum phosphorous 1.5 mg/dl (N 4-7), alkaline phosphatase 2100IU/L (N 57-180), SGOT 26 IU/L (N 5-40); SGPT 47 IU/L (N 5-45), serum uric acid 1 mg/dl (N 2-7) and fasting blood sugar of 75 mg/dl (N 65-110). The arterial blood gases revealed a persistent metabolic acidosis with bicarbonate ranging from 11-13 meq/L and pH from 7.22 to 7.27 with a simultaneous urinary pH of 5.5. Her serum sodium was 132 meq/L, potassium 3.8 meq/L, and chlorides 105 meq/L.

In the hospital she was found to have polyuria (2 L/24 hours). Urinalysis revealed a proteinuria of 1+ and glycosuria of 4+. She had a generalized aminoaciduria with alanine, threonine (++), serine, glutamic-acid, glycine and lysine being present. There was an excessive loss of several solutes in the urine as measured in a 24 hours' collection *(Table I)*. The tubular reabsorption of phosphorous (TRP) was calculated from a 2 hour collection of urine from 8 a.m. to 10 a.m. after an overnight fast while the serum phosphorous was esti-

TABLE I-*Urinary Solute Excretion in 24 Hours.*

	Patient	Normal
Na^+ (mmol)	225	40-220 (diet dependent)
K^+ (mmol)	57	2.5-125 (diet dependent)
(meq/kg/d)	7.6	(0.4-5.2)
CI- (mmol)	165 mmol	15-40 (diet dependent)
Ca^{++} (mg)	240	
(mg/kg/d)	32	<4
P (mg)	188	variable-diet dependent
Uric acid (mg)	714	520 ± 147
Glucose (g)	32	<0.5

mated from a blood sample at 9 a.m. The TRP was 92% (N>85%) and $TmPO_4$/GFR calculated was 2.1 mg/100 ml of GFR (N 2.7-5.6 mg/dl). The oral glucose tolerance test and serum ceruloplasmin levels were within normal limits.

Radiographs of her wrists revealed florid rickets with cupping, splaying and fraying of the radial and ulnar ends. Ultrasonography of the abdomen revealed mild hepatomegaly and normal sized kidneys with no evidence of nephrocalcinosis. Slit lamp examination of her eyes revealed no cystine crystals. Liver biopsy showed normal liver tissue with no evidence of a storage disorder.

Therapy was started with sodamint tablets (8 meq/kg/d), Joule's solution (P=750 mg/day) and 1-OH-cholecalciferol (0.25 µg/d) along with antibiotics for her respiratory infection. The high phosphorous dosage led to diarrhea and the dosage had to be reduced. After 2 months, her ABG showed a pH of 7.36 with a HCO_3 of 20.9 meq/L. Her serum calcium was 8.9 mg/dl, phosphorous 5.4 mg/dl and alkaline phosphatase 565 IU/L. clinically the anterior fontanelle closed and the child could sit up with a straight back. The hypotonia had decreased. Her weight and height showed no improvement.

Discussion

The association of severe growth retardation and resistant rickets with polyuria, metabolic acidosis, glycosuria, generalized aminoaciduria, hyperuricosuria and a low $TmPO_4$/GFR led to the diagnosis of Fanconi Syndrome in this child. The clinical examination and investigations failed to reveal a secondary cause for the disease such as galactosemia, Lowe's Syndrome, Wilson's disease or cystinosis. The presence of hepatomegaly and heavy glycosuria led to the suspicion of Type XI glycogen storage disease. However, as the child had no hypoglycemia and had normal liver function tests, normal glucose tolerance test and no storage disease on liver biopsy, this possibility was also excluded. Some of the uncommon features seen in this child were a marked hypercalcuria, a normal TRP and an inability to lower the urinary pH below 5.5 in the presence of a severe metabolic acidosis.

Patients with Fanconi Syndrome, in the presence of severe metabolic acidosis, can elaborate an acidic urine as the serum bicarbonate which is now below the threshold level stops leaking and the distal acidification mechanism is intact. However, this child showed an inability to lower the urinary pH below 5.5 despite having a serum bicarbonate of 11 meq/L, indicating the coexistence of a distal acidification defect. It has been suggested that in the presence of long standing Fanconi Syndrome, the distal acidifying mechanisms may also get altered.The exact cause is unclear. It may be related to potassium or phosphate depletion(3-5).

Most cases of Fanconi Syndrome have a low TRP (below 80-85%). Although the TRP of 92% in this child appears to be within normal limits, the findings of phosphaturia (fractional excretion of 8%) with a low serum phosphorous of 1.5 mg/dl is in itself abnormal. With intact tubular functions, there should be virtually no phosphorous excretion in the presence of low serum phosphorous especially below 2 mg/dl. The $TmPO_4$/GFR which is a better indicator of phosphorous reabsorption than TRP was very low in this child.

Hypercalciuria is usually not a feature of Fanconi Syndrome. This child had an unusually severe hypercalciuria (34 mg/kg/d) which may be secondary to the metabolic acidosis or due to the tubular dysfunction itself. Occasional cases of Fanconi's have been described with hypercalciuria(3.5).

Although Primary Fanconi Syndrome has not been reported in India, several reports exist in Western literature(6-ll). However, it should be remembered that as yet unidentified metabolic defects may be responsible for some of these cases. Primary Fanconi Syndrome currently remains a diagnosis of exclusion. The diagnosis can be easily missed unless appropriate investigations are undertaken in patients with failure to thrive and resistant rickets.

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