Dent’s Disease Presenting as Hypophosphatemic Rickets

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Background:
- Dent’s disease is a rare X-linked recessive disorder of the proximal tubule (PT) characterized by low molecular weight proteinuria, rickets, nephrocalcinosis, hypercalciuria and progressive renal insufficiency.
- Mostly caused by mutations in CLCN5 gene resulting in inactivation of the voltage gated chloride transporter in proximal tubule.
- Prevalence is unknown; reported in around 250 families to date.
- We report a case of hypophosphatemic rickets due to Dent’s disease with rapid progression to ESRD.

Case Description:
- A 16 year old Mexican male with no PMH presented with short stature, knock knees and walking difficulty.
- He had difficulty walking since 8 years of age which was explained as due to pes planus. However, this has progressed gradually to the point where he walks with extreme difficulty.
- Patient was born term, to non-consanguineous parents, and had normal birth weight and developmental milestones.
- Family history is significant for kidney and bone disease in most of his male cousins.

Physical Examination:
- Vital signs: BP 92/48 mmhg, Height53.8 cm (<3rd percentile), Weight 58.6 Kg (5th percentile), head circumference 54.5 cm (15th percentile).
- General: In no acute distress. Non dysmorphic.
- HEENT: Head Symmetric. No evidence of mucosal pallor or ANA were within normal limits.
- Weight 58.6 Kg (5th percentile), head circumference 54.5 cm (15th percentile).

Laboratory Data:
- Creatinine 1.6 mg/dl (N 0.5-1.06)
- GFR 60 ml/min
- BUN 18 mg/dl (N 5-20)
- PTH 912 pg/ml (N 9-69)
- 25 OH Vit D 12 ng/ml (N 20-100)
- ALP 1427 IU/L (N 65-260)
- Calcium 8.7 mg/dl (N 8.9-10.7)
- Phosphate 1.9 mg/dl (N 2.5-4.8)
- CBC, Serum Na, K, albumin, lipid panel, complement level and ANA were within normal limits.

Urinalysis
- Urine protein total: 2419 mg/hr with multiple increased amino acids (N 30-150)
- Urine calcium total: 98.9 mg/hrs (N 50-100)
- Urine phosphate total: 1250.8 mg/hrs (N 400-1100)
- Urine creatinine: 218.1 mg/dl (N 35-92)
- Urine calcium creatinine ratio: 0.2

Imaging:
- Bone X-rays
  - Delayed bone age at 14 yrs.
  - Generalized osteopenia with lucent metaphysis in large and small bones.
  - Concern for possible metabolic bone disease.

Kidney Ultrasound
- Bilateral cysts.
- Mild cortical thinning.
- Nephrocalcinosis.
- Mild right renal atrophy.

Genetic Testing:
- Positive for homzygous E112X mutation in CLCN5 gene, which confirmed the diagnosis of Dent’s disease.
- Negative for FGF23 and PHEX genes, which ruled out hypophosphatemic vitamin d-resistant rickets.

Clinical Course:
- Patient was diagnosed with Dent’s disease.
- He was started on Enalapril, K-phosp and Vit D3.
- Patient progressed to ESRD in 2 years and developed secondary hyperparathyroidism.
- He was started on peritoneal dialysis, underwent subtotal parathyroidectomy, and listed for kidney transplant.

Discussion:
- Dent’s disease (X-linked recessive nephrolithiasis) is a very rare genetic disorder.
- females carriers are usually asymptomatic, but some have osteopenia, decreased bone mineral density, and hypercalciuria.
- The prevalence is unknown; reported in around 250 families to date.
- We report a case of hypophosphatemic rickets due to Dent’s disease with rapid progression to ESRD.
- Dent’s disease is a very rare genetic disorder.

Clinical Manifestations:
- Dent’s disease has different clinical manifestations of which only low molecular weight proteinuria is the constant feature.
- Other clinical features include:
  - Renal failure: 64%
  - Rickets: 30%
  - Hypercalciuria: 95%
  - Nephrocalcinosis: 74%
- Our patient was diagnosed with Dent’s disease based on hypophosphatemic rickets, proteinuria, progressive renal failure, significant family history and confirmed with genetic testing.
- Approximately 1/3 of affected males develop some degree of renal insufficiency, which is generally apparent by late childhood.
- Still unclear as to exactly why and what proportion of sufferers progress to end stage renal failure.
- The progression could be partially due to infection and obstruction associated with nephrocalcinosis. However, some patients have reached ESRF with no evidence of nephrocalcinosis.
- In the largest study of patients with Dent’s disease, 9 of 15 men and 1 of 10 women reached ESRF at a mean age of 47 years.
- Our patient however developed ESRD and was started on peritoneal dialysis within 2 years of diagnosis, at 18 years of age.
- Most treatment measures are supportive, targeted at preventing nephrocalcinosis and enhancing bone health, with:
  - Thiazides and sodium restriction
  - Phosphate and Calcitriol supplementation
- Patients with ESRD do well on dialysis and are excellent candidates for renal transplantation.
- Calcium restriction is not recommended as it may increase bone disease.

Conclusion:
- Although Dent’s disease is now well reported and the genetic mutations responsible have been identified, there is still no clear strategy for the management of patients other than supportive measures.

References:

Bone X-rays showing osteopenia and delayed bone age

Ultrasound of right kidney showing cysts, renal atrophy and cortical thinning

Kidney Ultrasound