Case Report

Hypercalciuria and nephrolithiasis on long- term follow-up of Pseudo-vitamin D deficiency rickets

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Abstract

A case of pseudovitamin D deficiency (Vitamin D dependent rickets type I) is presented, who initially responded to physiological doses of calcitriol but developed nephrolithiasis and hypercalciuria around puberty. Hypercalciuria was corrected after stopping calcitriol.

Pseudo vitamin D deficiency rickets also called vitamin D dependent rickets type I (VDDR 1) is an uncommon cause of rickets. Patients appear normal at birth and manifests with signs between the ages of two months to two years. Muscle weakness is prominent, radiographic features are striking and response to calciferols is complete.[1,2] Hypercalciuria and nephrolithiasis are uncommon in the untreated disease but can develop due to overtreatment with calcitriol or oral calcium.[3] Here we report a patient who developed hypercalciuria and nephrolithiasis around puberty while on maintenance dose of calcitriol and oral calcium.

Case Report

A -15-year girl was evaluated at the age of 5 years for lower limb deformities. She was the second child of her non consanguineous parents, was born full term and had no perinatal insult. She had been weaned at appropriate age and had a normal physical and mental development. At age 4 years; her parents noticed deformities in her lower limbs. The child was diagnosed to have rickets and treated with 3.6 million units of vitamin D (six lac units weekly intramuscularly over a period of six weeks). There was no clinical or radiological evidence of improvement over the next one year. She was referred to the endocrinology for further evaluation. Examination revealed height of 105 cms [50th percentile by Indian Council of Medical Research (ICMR) standards] with upper segment to lower segment ratio of 1:1 and weight of 17 Kgs (50th percentile by ICMR standards). She had signs of rickets in the form of widening of wrists, rachitic rosary and knock knees. Investigations revealed normal complete blood count (CBC), liver and kidney functions. Bone function tests revealed a serum calcium of 8.9 mgs/dl, (normal value of 9.5-11.5mgs/dl), phosphorus of 4.3 mgs/dl (normal value of 5-7mgs/dl for her age) and alkaline phosphatase of 611U/L (normal value 30-120 in adults). X-ray wrist revealed changes of rickets (Figure-1), Pelvic x-ray revealed looser, s zones in superior and inferior pubic ramie. She was evaluated for non nutritional rickets. She had no evidence of renal tubular acidosis or Fanconi syndrome. Serum 25- hydroxy vitamin D was 100 ng/ml (normal value 8-80), 1, 25 dihydroxy vitamin D was less than 5 pg/ml (normal value16-65). Serum concentrations of 25-hydroxy vitamin D and 1, 25

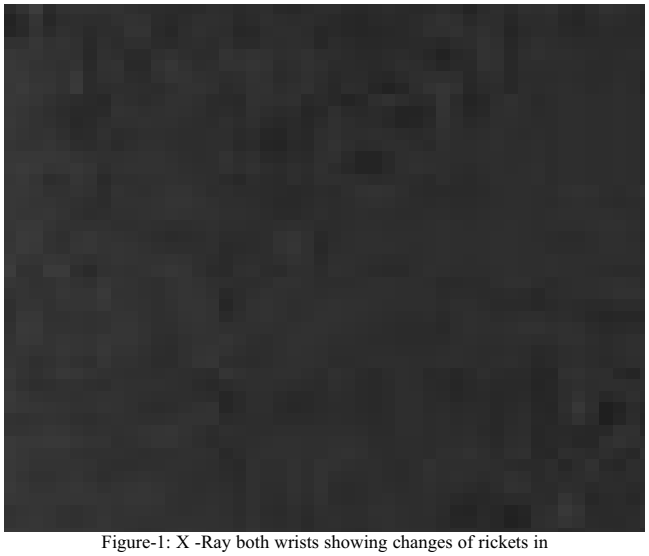

Figure-1: X -Ray both wrists showing changes of rickets in distal ends of Radius and Ulna.

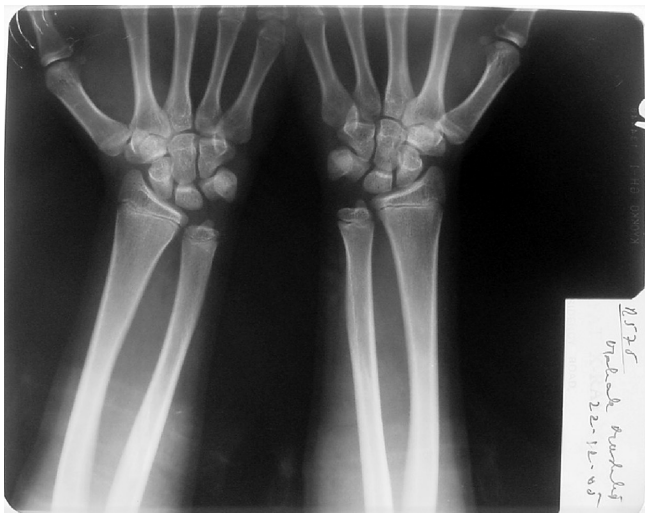

Figure-2: Follow up X -Ray both wrists showing complete resolution of changes of rickets.

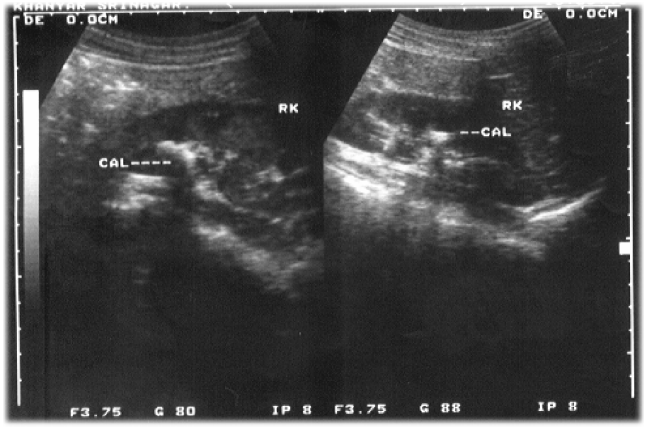

Figure-3: Ultrasonography of kidneys showing bilateral nephrolithiasis.

dihydroxy vitamin D were measured by specific radioimmunoassay. In view of clinical and radiological evidence of rickets, no response to massive doses of vitamin D, high Serum 25- hydroxy vitamin D and undetectable 1, 25 dihydroxy vitamin D a diagnosis of pseudo vitamin D deficiency rickets was made. She was started on calcitriol 0.25 g/day and elemental calcium 500mgs/day. The patient was next seen after four months and had a marked clinical and radiological improvement (Figure-1). At the age of 11 years dose of calcitriol was increased to 0.5 g/day and calcium to 750mg/day with monitoring of serum calcium every 3-6 months which were within normal limits. Meanwhile the girl attained menarche at the age of 13 years. At the age of 14 years she developed left flank pain and haematuria. Ultrasonography revealed multiple stones biggest being around 0.87×0.79mm in right middle and lower calyces without any hydronephrosis (Figure-2). Urine analysis revealed hypercalciuria on multiple occasions (urinary calcium of 365-633mgs/day (normal up to 200mgs/day). Serum calcium was 10.51 mgs/dl (Normal value 9.5-11.5mgs/dl). Calcitriol and oral calcium were stopped, which lead correction of hypercalciuria. Repeat ultrasonography did not reveal any further increase in size of the previous stones or formation of new stone. Patient is off calcitriol and calcium for one year now and is under follow up with monitoring of serum calcium, phosphorus and alkaline phosphatase and urinary calcium and phosphorus. During follow up her serum calcium remained around 8.24 to 8.9mgs/dl and 24 hour urinary calcium excretion was around 4.92-8 mgs/day and no new radiological changes of rickets/osteomalacia have appeared.

Discussion

Rickets is characterized by impaired mineralization of the bone matrix in growing children as a result of defects in the action of vitamin D.[4] Vitamin D undergoes sequential changes first in liver to form 25-hydroxyvitamin D [25(OH)D] and subsequently in kidney to form 1α,25-dihydroxyvitamin D [1 , 25(OH)$_2$D]. The latter action is mediated by 1 -hydroxylase mainly localized in the proximal tubules of the kidney.[5] 1 , 25-dihydroxyvitamin D binds to vitamin D receptor and induces several actions including regulation of calcium homeostasis.[6] Abnormalities in these actions result in hypocalcaemic rickets.

Our present patient had clinical and radiological evidence of rickets and osteomalacia with low serum calcium, phosphorus and mild increase in alkaline phosphatase with elevated 25(OH)$_2$D and undetectable 1, 25(OH)$_2$D. Her rickets which did not respond to massive doses of vitamin D, was corrected completely with physiological doses of calcitriol. So VDDR 1 was the most likely diagnosis. The disorder has been called as pseudovitamin D deficiency rickets, hereditary VDDR 1 and is an uncommon cause of hereditary rickets.[1,2] The gene for 25(OH)D 1α-hydroxylase has been mapped to chromosome 12q13.3.[7] Massive doses of vitamin D (100 to 300 times the recommended daily dose) are required to maintain remission in these patients as against a normal physiological dose of 1,25(OH)$_2$D$_3$ of 0.25-1μg per day.[8]

Nephrolithiasis and hypercalciuria are uncommon in untreated pseudovitamin D deficiency rickets but can very well develop during treatment. Deficiency of 1α-hydroxylase leaves the bioavailability of total 1α, 25(OH)$_2$ D unregulated, thus these patients adapt to the fluctuations in the calcium availability through direct actions of PTH alone.[3] Since intestinal fractional calcium absorption cannot be regulated by endogenous mechanisms, all the external calcium balance is regulated

at renal level only.[9] Thus patients may show a rapid fall or rise of urine calcium at times of under and over treatment respectively. The best way to minimise these fluctuations is to include a fixed calcium supplement of 1000mgs per day of elemental calcium.[3] Our patient developed hypercalciuria and nephrolithiasis around the age of puberty while on a maintenance dose of calcitriol and oral calcium. Thus clinicians treating these patients need to be aware that nephrolithiasis, nephrocalcinosis or both can develop during treatment even with maintainence dose of calcitriol and oral calcium especially around puberty. Periodic serum and urine calcium estimations and imaging will help prevention or early recognition of this complication and should be included in the routine follow up in these patients.

To conclude pseudovitamin D deficiency rickets is an uncommon genetic disorder getting corrected with physiological doses of calcitriol. Nephrolithiasis and hypercalciuria can occur even on small doses of calcitriol and oral calcium especially around puberty.

References

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