

Rickets: It is Not Always Nutritional. A Rare Case of Vitamin D-Dependent Rickets (VDDR) Type I

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Abstract

Rickets is typically due to nutritional cause, namely vitamin D and calcium deficiency worldwide. When there is suboptimal response to conventional vitamin D and calcium supplementation, alternative causes have to be sought. We report a rare case of vitamin D-dependent rickets (VDDR) who presented with rachitic features but normal total 25-hydroxyvitamin D 25(OH)D level. Conventional inactive vitamin D supplementation was ineffective and high dose of alfacalcidol was required to maintain normocalcaemia.

Keywords: Rickets; Nutritional; Vitamin-D; Hypocalcemia.

Case presentation

M was a 10 months old boy who was born full-term from, consanguineous Pakistani parents. Patient had uneventful antenatal and postnatal history. Boy enjoyed good past health except an episode of rhinovirus bronchiolitis at 4 months of age, had a complete recovery. Patient was admitted to our Pediatric unit for second episode of bronchiolitis. On admission, measurement was 73cm tall (25th centile) and weighed 8.5kg (25th centile). Boy had a respiratory rate of 32/min, oxygen saturation of 99% on room air, chest showing mild in sucking and bilateral end-expiratory wheeze. Boy

responded to bronchodilator treatment with resolution of wheeze the next day. Incidentally fraying of humeral joints were noted in chest X-ray. Physical examination of the patient showed frontal bossing, bilateral wrists and ankles swelling, rachitic rosaries and also generalized hypotonia. Similar rachitic changes were revealed in X-ray wrists and knees, showing fraying of distal radius and ulnar, femur and tibia. Blood tests showed severe hypocalcemia with plasma calcium 1.27mmol/L (2.31-2.64) only, ionized calcium (iCa) 0.71mmol/L (1.13-1.32), phosphate (PO₄) 1.02mmol/L (1.33-2.06), magnesium 0.66mmol/L (0.70-0.95) and alkaline phosphatase (ALP) raised to 1151U/L

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(122-469) as shown in Figure 1. Urine calcium/creatinine ratio was 0.3 which was normal. Patient was started on intravenous infusion of calcium 1mmol/kg/day in view of severe hypocalcemia. Boy was started on oral calcium carbonate (CaCO_3) 200mg six-hourly (elemental calcium 38mg/kg/day) and calciferol 2000 units daily at the same time as described in Figure 2. Calcium level rose to 1.84mmol/L after one day of intravenous calcium therapy. With the improvement of chest condition, parents demanded an early discharge despite medical advice on possible serious complications of severe hypocalcemia. Intravenous calcium infusion was stopped and oral CaCO_3 was stepped up to 500mg Q6H (elemental calcium 96mg/kg/day) before discharge.

At that time patient provisional diagnosis was nutritional rickets, which is rather common in our locality especially with the ethnicity of our patient. Boy was added on alfacalcidol (1 α -hydroxycholecalciferol) with dosage titrated to 0.8 microgram daily (95ng/kg/day) aiming for a quicker rise in calcium level, with the plan to take off early when calcium level stabilized.

An early follow-up was arranged with blood check. Follow-up blood check only three days after discharge showed a fall in calcium level again with calcium 1.50 mmol/L, iCa 0.81mmol/L, PO_4 1.13mmol/L, ALP 1254 U/L, parathyroid hormone (PTH) 35pmol/L (1.6-6.9) and urine calcium/creatinine ratio 0.57. Parents also reported two episodes of suspected tetany or seizure at home with sudden hands fisting and twitching for one minute which was self-aborted. Patient was

arranged urgent admission for the management of severe hypocalcemia. Doctors started to give intravenous calcium infusion again of calcium content 1mmol/kg/day. Calcium rose quickly to 2.06mmol/L after given one day of intravenous calcium, and then 2.33mmol/L the next day as shown in Figure 1. Intravenous calcium was continued for 2 more days as plasma calcium and ionized calcium dropped to 2.01 and 1.07mmol/L respectively after intravenous calcium was stopped. Subsequent investigations came back around two weeks since the clinical diagnosis of rickets, showing total 25-hydroxyvitamin D 25(OH)D 127nmol/L which refuted the diagnosis of nutritional vitamin D deficiency. Patient was suspected to have vitamin D-dependent rickets (VDDR). Calciferol was taken off since vitamin D deficiency was excluded. Calcium level was maintained when CaCO_3 was titrated to 2000mg Q6H (elemental calcium 430mg/kg/day) and alfacalcidol to 5 micrograms daily (600ng/kg/day). Calcium was 2.29mmol/L upon discharge. Subsequent follow-up was arranged after discharge, with serial monitoring of calcium levels being stable and on high side.

CaCO_3 was taken off four months after discharge and alfacalcidol was down-titrated to 2 micrograms daily (240ng/kg/day). ALP was normalized from a peak of 1330U/L to latest 389U/L. Parathyroid hormone was normalized to 1 pmol/L. Renal ultrasound was performed showing no nephrocalcinosis. Molecular study displayed a homozygous likely pathogenic variant in CYP27B1 gene confirming the diagnosis of vitamin D-dependent rickets type 1A.

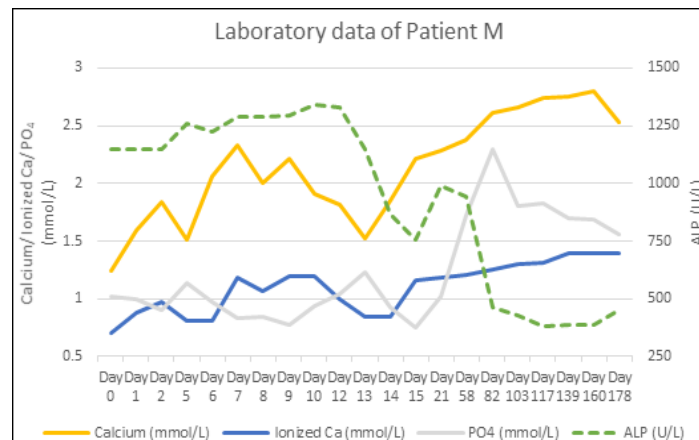


Figure 1: Laboratory data of Patient M.

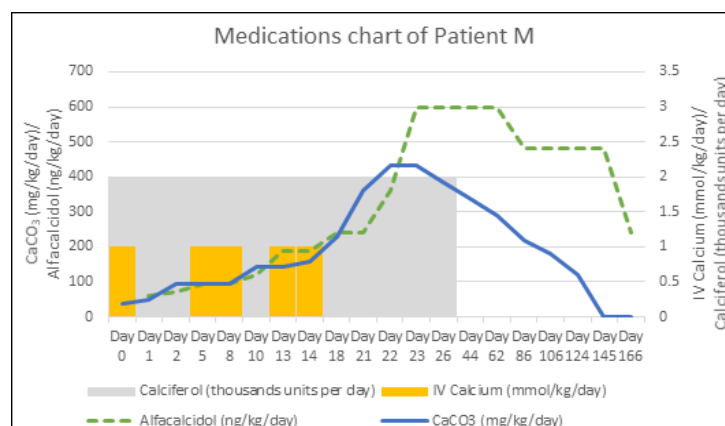


Figure 2: Medications chart of Patient M.

Discussion

Vitamin D is a fat-soluble vitamin which is present in two forms, ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) produced by plants, animals or formed in human skin by ultraviolet light. Two-step hydroxylation is then required for both forms of vitamin D. Vitamin D is first hydroxylated into 25(OH)D in the liver, and secondly 25(OH)D is further hydroxylated by 1 α -hydroxylase in the kidney to the biologically active 1,25(OH)₂D. Vitamin D-dependent rickets (VDDR) is a group of inherited inborn error of vitamin D metabolism due to mutation in different enzymes in the vitamin D metabolism pathways. There are three

board groups including type I- inability to fully activate calciferols, type II- vitamin D receptor defect and type III- excessive inactivation of vitamin D [1]. Our patient with genetic mutation in the CYP27B1 gene belongs to VDDR type IA, or vitamin D 1 α -hydroxylase deficiency, where after calciferols are activated to 25(OH)D, there is inability to further activate into 1,25(OH)₂D, the active vitamin D which binds to and activate vitamin D receptor. Clinical findings include hypotonia, growth failure, rachitic changes on examination and X-rays, hypocalcemia and hypophosphatemia but with normal to high total 25(OH)D. Both rachitic changes and hypotonia were present in our patient but fortunately has normal

growth on presentation. VDDR 1A is inherited in an autosomal recessive manner and therefore with a family background of consanguinity as in our case, high index of suspicion should be maintained. Clinicians should bear in mind the physiology of vitamin D and the possibility of vitamin D-dependent rickets when there is unfavorable clinical response to usual doses of vitamin D supplement.

This case illustrates the diagnostic difficulty of VDDR as rickets caused by vitamin D deficiency is much more common, especially in ethnicities with darker skin complexions. The biochemical parameters are similar in both nutritional and vitamin D dependent rickets with hypocalcemia, hypophosphatemia, high ALP and high parathyroid hormone. The only two most useful parameters helping the diagnosis of VDDR are a normal-to-high total 25(OH)D profile and a low 1,25(OH)₂D profile. Unfortunately, the slow turn-around time of total 25(OH)D profile in our locality (4 weeks) eliminated the possibility of checking the second-tier 1,25(OH)₂D level after patient was replaced with the vitamin D supplements. To supplement, 1,25(OH)₂D testing is a self-financed item by private laboratories locally. Alfacalcidol replacement would make the testing unreliable.

Concerning the treatment of patient, doctor had difficulty in maintaining a normal calcium level initially before alfacalcidol was stepped up to an extra high dose. VDDR 1A is due to failure to activate 25OHD to 1,25(OH)₂D and therefore inactive vitamin D supplement calciferol alone (25OHD) is unable to correct hypocalcemia. Active vitamin D, either calcitriol or alfacalcidol, calciferol analogues which bypass the need of 1 α -hydroxylation, is the mainstay of

treatment for VDDR 1A. With the initial clinical diagnosis of nutritional rickets, conventional doses of calcium supplement (50-100mg/kg/day) and inactive vitamin D calciferol 2000 units daily [2] was started. Alfacalcidol is not a routine treatment for nutritional rickets. It was added for our patient for severe hypocalcemia and that early discharge was undesirably unavoidable. For treating neonatal hypocalcemia or hypoparathyroidism, doctors usually keep the dosage of alfacalcidol at around 50-100ng/kg/day [3] as in our patient. Not until patient's vitamin D profile revealed a normal total 25(OH)D level, the diagnosis of VDDR became evident. The treatment regimen of VDDR is very different from nutritional rickets where the former is not responsive to inactive vitamin D and requires extraordinarily high dose of calcitriol or alfacalcidol, up to 2-3 micrograms daily [1,4,5] or 10-400ng/kg/day [6], which is 4-8 times of usual treatment dosage. For our patient, calcium level was only maintained with the dosage of alfacalcidol up to 5 micrograms daily (600ng/kg/day) and was latest titrated to 2 micrograms daily (240ng/kg/day). The treatment goals for VDDR are to maintain normocalcemia, to maintain normal PTH level and to avoid hypercalciuria. Regular ultrasound surveillance should be performed to look out for complication of nephrocalcinosis as it can occur even with normal level of serum calcium and vitamin D [7]. Doctors were able to near normalize ALP and PTH levels in three months' time, and quickly weaned off all calcium supplements to avoid hypercalcemia and hypercalciuria. For other types of VDDR, clinical features are similar except that 50% of the patients with VDDR 2 have alopecia [1,4]. Treatment are commonly challenging where extra high dose of oral calcium and oral calcitriol may be

required to restore normokalaemia. For VDDR 2 where there is vitamin D receptor defect, intermittent intravenous infusion of calcium may be necessary [1]. For these resistance cases requiring intravenous calcium infusion, prolonged hospitalization would be anticipated [8].

Summary

Doctors report a rare case of vitamin D-dependent rickets type IA, presenting with incidental finding of rachitic changes on chest X-ray and initial blood tests showing a typical

pattern in nutritional rickets (hypocalcemia, hypophosphatemia, raised ALP and PTH). Patient failed to respond to conventional doses of inactive vitamin D supplementation and was able to maintain normocalcaemia upon topping up the dosage of alfacalcidol. Patient's diagnosis was revealed after 25(OH)D result was available and with genetics result confirming the diagnosis. Clinicians should have heightened awareness when the response to conventional rickets treatment is suboptimal, especially in patients with consanguineous parents.

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