Instructive case

Acute respiratory failure and generalized hypotonia secondary to vitamin D dependent rickets type 1A

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1. Introduction

Vitamin D plays a major role in calcium homeostasis and bone mineralization. Vitamin D is a cholesterol derived pro-hormone which is available in two forms: ergocalciferol (D2) produced in plants and cholecalciferol (D3) produced in animal by the action of ultraviolet B radiation on 7-dehydrocholesterol in animal skin. Vitamin D undergoes sequential hydroxylation steps by cytochrome P-450 enzyme system to produce its active form. First hydroxylation takes place in liver due to 25 hydroxylase enzyme activity producing 25-hydroxy vitamin D [25(OH)D]; this is the most abundant circulating form of vitamin D. Active metabolite of vitamin D is produced by rate limiting step of 1α-hydroxylase enzyme in renal tubules producing 1,25-dihydroxyvitamin D [1,25(OH)2D]. 1-α-hydroxylase activity is tightly regulated by parathyroid hormone, calcium, phosphorus and 1, 25-dihydroxyvitamin D [1,2].

Hypocalcemic rickets is mainly due to either nutritional deficiency or genetic disorders of vitamin D. Nutritional rickets is caused by poor intake of calcium and vitamin D or lack of exposure to sun causing vitamin D deficiency. Genetic disorders of vitamin D dependent rickets include vitamin D dependent rickets type 1A (VDDR1A; MIM 264700) and vitamin D dependent rickets type 1B (VDDR1B; MIM 600081). The other genetic disorders cause resistance to vitamin D and include vitamin D dependent rickets type 2A (VDDR2A; MIM 277440) and vitamin D dependent rickets type 2B (VDDR2B; MIM 6007850).

Vitamin D dependent rickets type 1A (VDDR1A; MIM 264700) occurs due to mutation in CYP27B1 gene that codes for 1α-hydroxylase enzyme. The deficiency of 1α-hydroxylase enzyme results in inability to produce active vitamin D 1, 25-dihydroxyvitamin D [1,25(OH)2D]. Active vitamin D [1,25(OH)2D] binds to a nuclear receptor having ligand binding and DNA binding domains to produce target proteins [3].

Vitamin D dependent rickets type 1 A is a rare autosomal recessive disorder having a variable presentation at an early age...
A two-year-old boy was previously healthy until the age of one year. He was born full term with spontaneous vaginal delivery to consanguineous parents; birth weight was 2 kg (−2.5SD). Neonatal course was uneventful with exclusive breast feeding until the age of 6 months. He started rolling side to side and sitting with support at the age of 7 months. He was able to pull himself to standing at 12 months. He never walked on his own. Parents noted at the age of one that he was not progressing in motor development and not gaining weight. He developed clinical signs of rickets with widening ephipyses and bowing of long bones [4].

We present a case of a two-year-old boy presented with acute respiratory failure, severe hypotonia, hypocalcaemia and hypophosphatemia secondary to D dependent rickets type 1A.

2. Case history

A two-year-old boy was previously healthy until the age of one year. He was born full term with spontaneous vaginal delivery to consanguineous parents; birth weight was 2 kg (−2.5SD). Neonatal course was uneventful with exclusive breast feeding until the age of 6 months. He started rolling side to side and sitting with support at the age of 7 months. He was able to pull himself to standing at 12 months. He never walked on his own. Parents noted at the age of one that he was not progressing in motor development and not gaining weight. He developed clinical signs of rickets with widening ephipyses and bowing of long bones. He was diagnosed with nutritional rickets by his pediatrician and commenced on vitamin D3 supplements. He was fed with powdered milk (Nido) and regular solid food. He continued to regress in his milestones and lost the ability to sit or roll. He suffered several respiratory tract infections despite regular bronchodilator and steroid inhalers since the age of 1. He required two hospital admissions for respiratory symptoms. There is no available record of his bone profile from previous hospital admissions. He presented to the emergency room with severe respiratory distress requiring high oxygen via face mask. He was apathetic looking although did not have any obvious dysmorphic features. Physical examination revealed a malnourished child with weight of 6.8 kg (−6 SD) and length of 70 cm (−4.75SD). There were obvious signs of rickets including palpable widening of wrist and ankle joints, prominent forehead, soft skull bone, rachitic rosary and narrow bell-shaped chest (Fig. 1A). He had normal scalp hairs and eyebrows. He had generalized muscle wasting with severe hypotonia. He was unable to sit or roll side by side. His speech and cognitive function was appropriate for his age.

2.1. Investigations

He was admitted to pediatric intensive care unit and ventilated for 2 days for hypoxia and hypercapnia. Chest x-ray showed bilateral atelectasis and diffuse parenchymal haziness (Fig. 1B). He was weaned to CPAP and nasal oxygen to room air over 5 days.

He was investigated for rickets and hypotonia. Biochemical testing showed calcium 1.98 mmol/L (2.10−2.55), phosphate 0.33 mmol/L (1.00−2.00), alkaline phosphatase 538 U/L (0−281), parathyroid hormone 821 ng/L (10.0−65.0), 25 OH vitamin D 66 ng/ml (20−50), 1,25 OH vitamin D 39 pg/ml (24−86) and normal renal function, ammonia and lactic acid. Urine chemistry showed high renal calcium and phosphate excretion; calcium creatinine ratio 4.17 mmol/mmol, urinary phosphate 20.9 mmol/L with renal tubular absorption of 74%, X-ray of lower and upper limbs revealed severe osteopenia, cupping and fraying of long bones metaphysis and bilateral fibular mid-shaft fracture (Fig. 2A).

The differential diagnosis after the initial work up was vitamin D dependent rickets type 1 (VDDR1A), vitamin D dependent rickets type 2A and X-linked hypophosphatemic rickets. He did not have alopecia, which is present in the majority of cases with vitamin D dependent rickets type 2A [5]. Hypophosphatemic rickets is not usually associated with hypocalcemia and raised parathyroid hormone. 1.25 OH vitamin D level is although within normal reference range but with the severity of hypocalcemia and raised parathyroid hormone level it is considered as inappropriately low.

2.2. Management

The treatment was started with high suspicion of vitamin D dependent rickets type 1A. He was commenced on alfalcacidol, oral calcium and phosphate. He responded very quickly to oral therapy and calcium normalized in two days. We also placed a port-a-cath for intravenous calcium infusion. High dose calcium infusion protocol for vitamin D dependent rickets type 2A [6] is followed due to severe clinical and radiological picture to achieve rapid improvement. Serum calcium was closely monitored and kept in lower normal range. Two weeks after calcium infusion urinary calcium creatinine ratio was 0.92 mmol/mmol. Calcium infusion continued for one month; at the end of therapy there was no nephrocalcinosis on renal ultrasound. Laboratory testing showed calcium 2.27 mmol/L (2.10−2.55), phosphate 1.13 mmol/L (1.00−2.00), alkaline phosphatase 1532 U/L (0−281) and

![Fig. 1. A: Narrow bell shaped chest with rachitic rosary. B: Bilateral atelectasis and parenchymal haziness.](image-url)
parathyroid hormone 65.4 ng/L (10.0–65.0). There was complete resolution of respiratory symptoms and marked improvement in muscle tone as he started rolling and sitting. He was discharged home on oral alfacalcidol and calcium.

2.3. Follow up

At three months follow up, he was maintaining bone profile and parathyroid hormone in normal range and improved alkaline phosphatase. X-ray of lower limb showed improvement in the signs of rickets and healing of fibular fracture. He started walking without support and did not have any respiratory symptoms.

2.4. Genetic testing

Vitamin D dependent rickets has mutation in CYP27B1 gene coding for 1α hydroxylase protein. Our patient DNA analysis showed homozygous mutation p.Arg429Pro (R429P) at exon c.1286 G>C. This mutation is previously reported and shown absence of detectable in vitro activity of 1α hydroxylase protein [7].

3. Discussion

Vitamin D dependent rickets type 1 is a rare autosomal recessive disorder which is more prevalent in societies with high number of inter-family and consanguineous marriages. We reported the case of a two-year-old boy that has history of typical rickets presenting at the age of 1 year but did not respond to Vitamin D3 supplements. He deteriorated over 1 year with severe hypotonia and recurrent respiratory symptoms requiring hospital admissions. The diagnosis is delayed because there is high prevalence of vitamin D deficiency in Saudi population therefore clinicians have low clinical suspicion to consider other differential diagnosis of rickets. Genetic testing revealed homozygous mutation in CYP27B1 gene. He responded very quick to oral alfacalcidol and calcium therapy. Motor milestones and hypotonia improved within 3 months of treatment.

Vitamin D deficiency is a major global health issue. A systemic review of 103 studies from different global regions has shown highest prevalence of Vitamin D deficiency in Middle East among all age groups and particularly in adolescent girls and women. Adolescent female in Saudi Arabia has 81% prevalence of Vitamin D deficiency [8]. Children presenting with rickets in this region are rationally diagnosed as nutritional rickets and commenced on vitamin D3; as compliance with the treatment is culturally not always adequate slow improvement would not immediately raise the suspicion of wrong diagnosis. Vitamin D level measurement is readily available but 1,25OH D measurement is available in few specialized centers.

Saudi Arabia has a high tradition of inter-family marriages particularly between first cousins. This tradition is part of Arab societies and their majority religion Islam permits inter-family marriages. This trend facilitates the families to keep their cultural and religious norms intact. First cousin and close relation marriages comprise 25–42% of marriages in Saudi society. International consanguinity workshop (2011) reports a consensus on association of congenital malformation and autosomal recessive diseases causing increased postnatal mortality in consanguineous marriages [9].

Our case has a striking finding of severe hypotonia associated with regressing milestones and respiratory symptoms due to proximal muscle weakness. Yun Yan et al. also reported a similar case of VDDR1 in infant with severe hypotonia [10]. Etiology of this severe hypotonia is contributed by direct effect of vitamin D on muscle fibers length and also due to hypophosphatemia causing decrease muscle strength. Muscle fibers of striated muscles are studied in vitamin d receptor null mice (VDR−/−) and compared with wild type; fibers are significantly smaller in VDR null mice [11]. Hypophosphatemia secondary to vitamin D deficiency and hyperparathyroidism plays major role in hypotonia as vitamin deficient mice do no show hypotonia as long serum phosphate and calcium level is maintained with in normal range [12].

CYP27B1 gene (MIM #609506) encodes for 1α hydroxylase enzyme. The human gene was first mapped at chromosome 12q14 by linkage analysis in 1990 and later on cloned in 1997 [13,14]. This gene contains 9 exons spanning 5 kb and eight introns. More than
50 mutations are reported to date including missense or nonsense mutations, deletions, splicing and duplications. Phenotype of VDDR1A can be modified by endogenous and exogenous factors other than gene mutation. Residual enzyme activity may cause only milder phenotype. Alzahrani et al. reported a large family with six siblings having a gene mutation but variable clinical and biochemical profile; three of them are clinically asymptomatic but biochemical profile is suggestive of disease while the other three has mild rickets and growth retardation [15].

4. Learning points

- Clinician should have a low threshold to consider rare genetic disorders in the differential diagnosis in societies with high rate of inter-family and consanguineous marriages.
- Vitamin D deficiency is a global phenomenon particularly in Middle East and is the most common cause of rickets; but children not responding to Vitamin D supplements should be considered for rare hereditary causes of rickets.
- Severe hypotonia and motor milestones regression is associated with rickets. Rickets should be considered in differential diagnosis of hypotonia along with neurological and metabolic conditions.
- Active vitamin D metabolites (alfacalcidol and calcitriol) therapy deserves regular screening for nephrocalcinosis and intraocular calcification.

Conflict of interest

We declare that we have no conflict of interest and we have not received any financial support for this case report.

Ethical statement

We have an informed consent from parents to publish this case without disclosing any personal identification.

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