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Case Report

Seizures and isolated motor delay in two siblings: looking beyond cerebral palsy

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ABSTRACT

Rickets is a metabolic bone disorder resulting from impaired mineralization of the growing skeleton and may present with nonspecific features such as motor delay, muscle weakness, and seizures. In some children, particularly when skeletal manifestations are subtle, the underlying metabolic cause may be overlooked and the presentation may initially be attributed to nutritional deficiency or a primary neurological disorder. We report two siblings born to consanguineous parents who presented with delayed gross motor milestones and features of rickets. The elder child additionally had hypocalcemic seizures. Both children demonstrated hypocalcemia, markedly elevated alkaline phosphatase and parathyroid hormone levels, normal-to-elevated serum 25-hydroxyvitamin D concentrations, and without renal phosphate wasting. They failed to respond to conventional vitamin D supplementation. Genetic analysis revealed a homozygous pathogenic duplication in exon 8 of the CYP27B1 gene, confirming the diagnosis of VDDR-IA. Treatment with calcitriol and calcium led to rapid biochemical normalisation and significant clinical improvement, culminating in independent ambulation on follow-up. This report emphasizes the importance of considering vitamin D dependent rickets in children with early-onset rickets and poor response to standard therapy, particularly in the presence of consanguinity or sibling involvement. Early genetic diagnosis enables targeted treatment and prevents prolonged morbidity.

Keywords: Vitamin D dependent rickets, VDDR type 1A, CYP27B1 mutation, Hypocalcemic seizures, Resistant rickets, Sibling cases, Calcitriol therapy

INTRODUCTION

Rickets is a disorder of the growing skeleton caused by defective mineralization of the epiphyseal growth plate due to disturbances in calcium and/or phosphate homeostasis, leading to growth retardation and skeletal deformities in children. It is most commonly related to vitamin D, calcium, or phosphate deficiency and are broadly classified into calciopenic and phosphopenic rickets.[1] Failure to respond to appropriate vitamin D and calcium supplementation should prompt consideration of resistant or inherited causes of rickets.

Vitamin D exists as vitamin D_3, synthesized in the skin following ultraviolet B exposure, and vitamin D_2, obtained from dietary sources.[2] Activation of vitamin D requires sequential hydroxylation in the liver and kidney, with the final step mediated by renal 1α-hydroxylase to generate the biologically active hormone, 1,25-dihydroxyvitamin D.[3] Defects in this activation pathway result in impaired calcium homeostasis and resistant forms of rickets.

Early descriptions of rickets date back to the 17th century, with accounts by Whistler and Glisson in the mid-1600s. The concept of vitamin D resistant rickets was later elaborated by Albright and colleagues in 1937,

followed by Prader's description of vitamin D dependent rickets in 1961. It is a rare autosomal recessive disorder caused by mutations in the CYP27B1 gene, which encodes renal 1α-hydroxylase.[4,5] Affected children typically present in early childhood with growth failure, delayed motor milestones, skeletal deformities, and hypocalcemic seizures, with characteristic biochemical findings of hypocalcemia, secondary hyperparathyroidism, elevated alkaline phosphatase, and normal or elevated serum 25-hydroxyvitamin D levels.[6]

We report two siblings with vitamin D–dependent rickets type 1A caused by a homozygous pathogenic variant in the CYP27B1 gene, highlighting the importance of considering this diagnosis in children with refractory rickets and poor response to conventional therapy.

CASE REPORT

Case 1

A 26-month-old boy was brought to our institute with complaints of inability to stand or walk for the past year and recurrent seizures. He was the first child born to parents in a second-degree consanguineous marriage. He was delivered by lower-segment cesarean section and had an uneventful perinatal period with an immediate cry at birth. He was exclusively breastfed until 6 months of age, after which complementary feeding was appropriately initiated.

Early developmental milestones were reported to be normal. He achieved head control at 4 months, rolled over at 5 months, and sat with support by 6 months. Language and social development were age-appropriate, with the child speaking two meaningful words by 12 months of age. However, from around 12 months of age, his parents noticed a delay in gross motor milestones, as he was unable to crawl, stand, or walk independently. Attempts to make him stand were associated with crying, following which he would immediately assume a sitting position.

At 13 months of age, he experienced a generalised tonic clonic seizure in the absence of fever. He was diagnosed elsewhere as having a simple febrile seizure and was treated with oral calcium supplementation in view of documented hypocalcemia, along with levetiracetam. A similar seizure episode occurred at 16 months of age, after which antiepileptic therapy was continued. Cognitive development remained appropriate for age. In view of isolated gross motor delay, a diagnosis of cerebral palsy was made elsewhere for which MRI of the brain was ordered and showed no abnormalities; physiotherapy was subsequently recommended.

Following initiation of physiotherapy, the child developed worsening discomfort, characterized by increased crying and further restriction of lower limb movements. At 16 months of age, he was evaluated at another hospital, where magnetic resonance imaging of the entire spine was performed to rule out spinal pathology and was reported as normal. He was subsequently advised oral vitamin D and calcium supplementation. However, despite this treatment, his motor milestones did not improve, and the child remained non-ambulatory by 26 months of age, prompting referral to our institute for further evaluation. There was no history of developmental regression, bowel or bladder incontinence, excessive thirst or urination, weight loss, limb thinning, easy bruising, or joint swelling. Tooth eruption began at 8 months of age, with no history of dental pain, caries, or enamel defects.

On examination, the child was alert, interactive, and responsive to his surroundings. Speech was meaningful and appropriate for the age. Cranial nerve examination was normal. He had normal upper-limb movements and was able to sit with minimal support, with both lower limbs extended at the knees. Attempts to make him stand elicited pain and crying. Generalised hypotonia was noted, with greater involvement of the lower limbs. Muscle bulk and deep tendon reflexes were normal, and sensory examination revealed no abnormalities. No trophic changes were observed.

The child had sparse, lightly pigmented scalp hair with bifrontal alopecia (Figure 1A), and the hair was easily pluckable. Musculoskeletal examination revealed classical features of rickets, including widening of the wrists (Figure 1C) and malleoli, bowing of the distal upper and lower limbs, rachitic rosary (Figure 1B, Harrison's sulcus, genu varum, and a protuberant abdomen. The thorax appeared bell-shaped with prominent beading of the costochondral junctions. Spinal examination revealed a right-sided scoliosis. Craniofacial features included frontal bossing and a widely open anterior fontanel measuring 4×3 cm. Dentition revealed only two upper and two lower central incisors, with normal enamel and no evidence of caries.

General examination revealed no abnormalities of the eyes or ears. A small mucocele was noted on the inner aspect of the lower lip. The abdomen was soft, protuberant, and lax, with no hepatosplenomegaly. External genital examination showed normally formed testes descended into the scrotum.

Anthropometric assessment revealed severe stunting and undernutrition, with a weight of 7.34 kg (<3rd centile), length of 74 cm (<3rd centile), head circumference of 47 cm (3rd–50th centile), and mid-upper arm circumference of 12.5 cm. The upper-segment-to-lower-segment ratio was 1.5:1, suggestive of disproportionate short stature. Frontal alopecia was observed in both the patient and his father, suggesting a familial phenotypic feature (Figure 1d).

Laboratory evaluation at our institute revealed severe hypocalcemia (total serum calcium 5.9 mg/dl; ionized

calcium 0.84 mmol/l), hypophosphatemia (2.8 mg/dl), mildly reduced magnesium (1.6 mg/dl), markedly elevated alkaline phosphatase (2427 iu/l), and normal renal function (serum creatinine 0.4 mg/dl). Parathyroid hormone levels were markedly elevated at 1028 pg/ml (reference range 10–55 pg/ml). Serum 25-hydroxyvitamin D level was elevated at 167.6 ng/ml. Venous blood gas analysis showed a pH of 7.34, a bicarbonate of 20 mEq/l, and a normal anion gap.

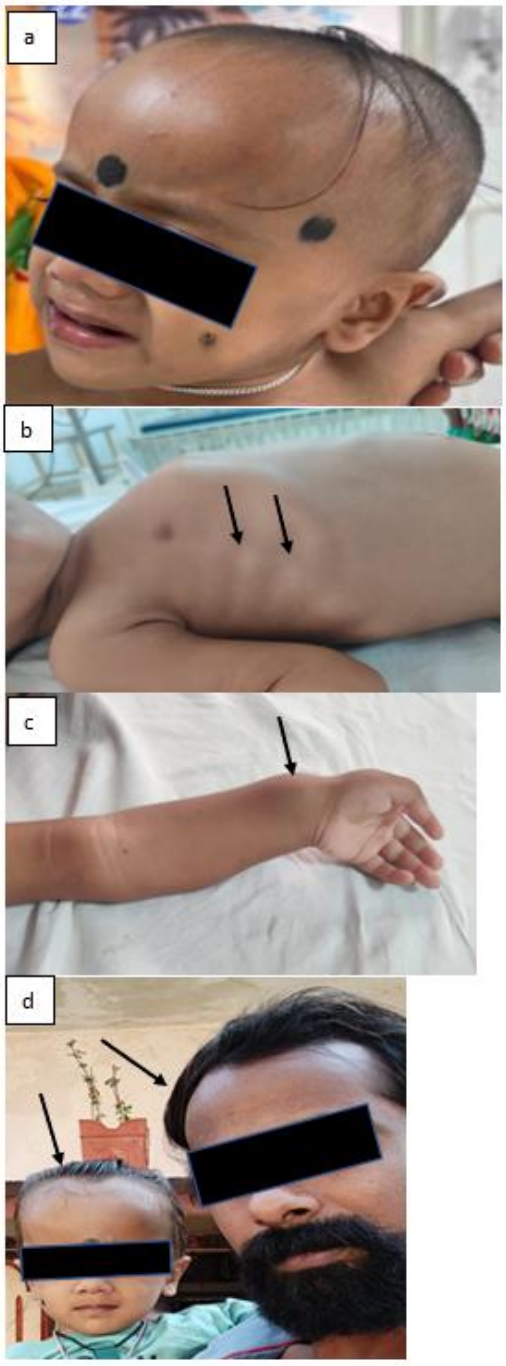

Figure 1: (a) frontal bossing with alopecia, (b) rachitic rosary of rib cage, (c) wrist widening, (d) father and child with alopecia.

Skeletal survey, including radiographs of the left wrist, hand, and both lower limbs, demonstrated diffuse physeal widening with marked metaphyseal cupping and fraying, along with pathological fractures of the left ulna and left tibia, findings suggestive of severe active rickets (Figure 2 a and b).

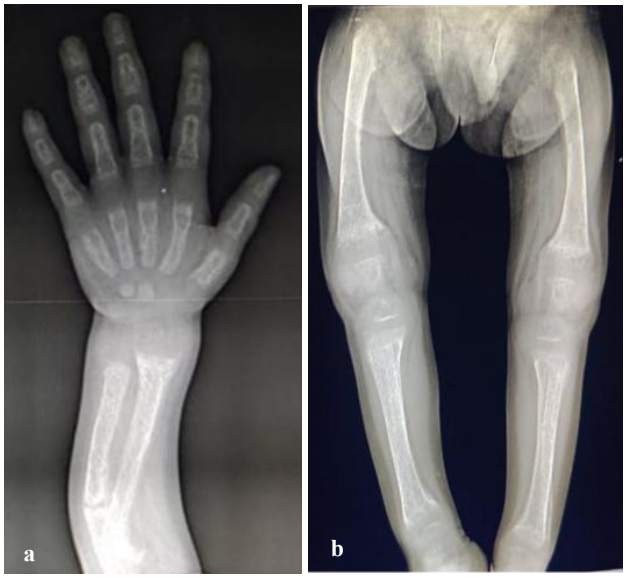

Figure 2: (a) Diffuse osteopenia showing widening of the physes with metaphyseal cupping, fraying, splaying and fracture of shaft of ulna, (b) left tibia.

Case 2

The younger sibling, a 14-month-old boy, was evaluated after the elder child was recognised to have similar symptoms. He was reportedly developmentally normal until 6 months of age, after which difficulty in crawling and standing with support was noted. He had one episode of generalised tonic-clonic seizures without fever at 13 months of age treated elsewhere symptomatically, treatment details not available. He was exclusively breastfed until 6 months of age, then introduced to appropriate complementary feeding. On examination, the child was alert, interactive, and developmentally appropriate for age, able to speak two meaningful words and reach for objects. Physical examination revealed features similar to those of his elder sibling, including frontal bossing with frontal alopecia, widening of the wrists and malleoli, and a Harrison's sulcus; however, skeletal deformities were milder. Anthropometric measurements showed a weight of 7 kg, length of 68 cm, and head circumference of 46 cm.

Laboratory investigations revealed hypocalcemia (6.6 mg/dl), mild hypophosphatemia (3.3 mg/dl), and a serum magnesium level of 1.8 mg/dl. Serum 25-hydroxyvitamin d level was elevated at 77.94 ng/ml. In both children, tubular reabsorption of phosphorus was normal (90%). Renal ultrasonography showed no evidence of

nephrocalcinosis, and liver function tests were within normal limits.

Radiographs of both lower limbs revealed diffuse physeal widening with metaphyseal cupping and fraying involving the distal femora and proximal tibiae, consistent with active rickets. No evidence of pathological fractures was seen.

Differential diagnosis: Nutritional vitamin D deficiency rickets; Vitamin D dependent rickets (resistant rickets); Hypophosphatemic rickets; Renal tubular disorders causing rickets; Malabsorption-related rickets; Neuromuscular disorders and cerebral palsy.

The combination of isolated gross motor delay, hypocalcemic seizures, and classical skeletal deformities initially suggested nutritional rickets. Still, it was excluded due to failure to respond to adequate vitamin D and calcium supplementation and to markedly elevated serum 25-hydroxyvitamin D levels. Hypophosphatemic rickets and renal tubular disorders were ruled out by normal tubular phosphate handling, absence of renal phosphate wasting or metabolic acidosis, and preserved renal function.

Malabsorption was unlikely given adequate nutrition, absence of gastrointestinal symptoms, and elevated vitamin D levels. Although neurological causes were considered, normal cognition and neuroimaging, pain on weight-bearing, and unequivocal clinical and radiological features of rickets confirmed a metabolic bone disorder. Early onset, sibling involvement with consanguinity, severe secondary hyperparathyroidism, and refractoriness to conventional therapy established vitamin D dependent (resistant) rickets and justified targeted genetic testing.

Targeted genetic testing was subsequently performed and identified a homozygous pathogenic CYP27B1 c.1319_1325dup (p.Phe443ProfsTer24) variant, confirming the diagnosis of vitamin D–dependent rickets type 1A (VDDR1A) (Table 1).

Table 1: Genetic analysis of case 1 showing a homozygous pathogenic CYP27B1 c.1319_1325dup (p.Phe443ProfsTer24) variant.

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
CYP27B1 (-) (ENST00000228606.9)	Exon 8	c.1319_1325dup (p.Phe443ProfsTer24)	Homozygous	Vitamin D-dependent rickets, type I (OMIM #264700)	Autosomal recessive	Pathogenic (PVS1, PM2, PP5)

Management and outcome

Based on the clinical presentation of isolated gross motor delay with seizures, classical skeletal features of rickets, and failure to respond to conventional vitamin D and calcium supplementation, a diagnosis of resistant rickets was considered after excluding common etiologies. This was subsequently confirmed by genetic testing.

The elder sibling (Case 1) was initially managed with intravenous calcium to correct severe hypocalcemia, followed by oral calcium and calcitriol therapy. The younger sibling (Case 2), who had milder biochemical abnormalities and no seizures, was treated with oral calcium and calcitriol from the outset.

Two months after therapy, both children demonstrated complete biochemical normalization, including serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels. Clinically, there was marked improvement in pain and muscle strength, with progressive weight-bearing. By six months of continued treatment, both children achieved independent ambulation.

DISCUSSION

Rickets is a heterogeneous group of disorders affecting the growing skeleton, resulting from defective mineralization of the growth plate due to disturbances in calcium and/or phosphate homeostasis.[7] Although vitamin D deficiency remains the most common cause worldwide, inherited forms of rickets should be considered in children with early-onset disease or failure to respond to standard therapy. Clinically, rickets commonly manifests with growth retardation, delayed motor milestones, skeletal deformities, muscle weakness, and, in severe cases, hypocalcemic seizures.[8]

From a pathophysiological perspective, rickets is broadly classified into calciopenic and phosphopenic forms based on the predominant mineral abnormality. Calciopenic rickets is most often caused by vitamin D deficiency or inadequate calcium intake, but may also result from

impaired vitamin D metabolism or resistance to its active form. Phosphopenic rickets, in contrast, is primarily caused by renal phosphate wasting and includes conditions such as X-linked hypophosphatemic rickets and other hereditary or acquired renal tubular disorders.[9,10] Failure to improve despite appropriate vitamin D and calcium supplementation should prompt evaluation for genetic causes of rickets.

Vitamin D dependent rickets (VDDR) represents a rare group of inherited disorders characterized by impaired vitamin D activation or resistance to its action.[11] The term vitamin D resistant rickets was first introduced by Albright and colleagues in 1937 to describe forms of rickets requiring vitamin D doses far exceeding those necessary to treat nutritionally deficient rickets.[12] Vitamin D activation requires renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the enzyme 1α-hydroxylase, encoded by the CYP27B1 gene. Defects in this step result in normal or elevated 25-hydroxyvitamin D levels with inappropriately low or low-normal 1,25-dihydroxyvitamin D, leading to vitamin D–dependent rickets type 1A.[13]

Four rare genetic defects affecting vitamin D metabolism and action have been described as causes of rickets. Vitamin D–dependent rickets type 1A (VDDR-1A) results from a deficiency of renal 1α-hydroxylase due to mutations in the CYP27B1 gene, leading to impaired conversion of 25-hydroxyvitamin D to its active form despite normal or elevated serum levels. VDDR-1B is caused by 25-hydroxylase deficiency secondary to mutations in the CYP2R1 gene. Vitamin D dependent rickets type 2A (VDDR-2A), also referred to as vitamin D–resistant rickets, results from mutations in the vitamin D receptor. In contrast, the rare VDDR-2B is caused by post-receptor signalling defects that interfere with normal vitamin D receptor function.[14]

VDDR type 1A is the most frequently reported subtype and typically presents within the first two years of life. Affected children commonly exhibit growth failure, delayed gross motor milestones, muscle weakness, bone pain, and classical skeletal deformities of rickets. Hypocalcemic seizures are a recognized early manifestation and may precede overt skeletal changes.[15] Biochemically, VDDR-IA is characterized by hypocalcemia, hypophosphatemia secondary to severe secondary hyperparathyroidism, markedly elevated alkaline phosphatase levels, normal or elevated serum 25-hydroxyvitamin D concentrations, and inappropriately low or normal levels of 1,25-dihydroxyvitamin D.[16]

The clinical and biochemical features observed in both siblings in the present report are highly consistent with VDDR-IA. Early onset of disease, isolated gross motor delay with preserved cognition, hypocalcemic seizures in the elder sibling, absence of renal phosphate wasting, markedly elevated parathyroid hormone levels, and lack of response to conventional vitamin D supplementation strongly suggested a defect in vitamin D activation rather than nutritional deficiency or phosphopenic rickets. The occurrence of disease in siblings born to consanguineous parents further supported an autosomal recessive etiology.

Genotype–phenotype correlation in VDDR-IA is variable, with considerable clinical heterogeneity reported even among patients harboring identical CYP27B1 mutations.[17] Truncating and frameshift mutations, including the commonly reported seven–base pair duplication in exon 8 of CYP27B1, are often associated with early onset and severe biochemical derangements.[18,19] However, intrafamilial variability is well recognized, as demonstrated in the present report, in which the younger sibling exhibited a milder phenotype than the elder child. This variability highlights the influence of modifying factors, such as age at diagnosis, calcium intake, and timing of calcitriol initiation, rather than genotype alone.

Management of VDDR type 1A requires replacement with the active form of vitamin D (calcitriol) and calcium supplementation, rather than nutritional vitamin D alone. Early initiation of appropriate therapy results in rapid biochemical normalization and significant improvement in motor function and skeletal manifestations.[20] These cases emphasize the importance of considering vitamin D dependent rickets among the differential diagnoses in children with rickets who fail to respond to routine vitamin D and calcium therapy. Increased awareness and timely genetic evaluation can prevent prolonged morbidity, unnecessary investigations, and misdiagnosis.

CONCLUSION

Vitamin D dependent rickets type 1A is a rare but treatable cause of refractory rickets in early childhood. This report highlights the need to consider VDDR-IA in children presenting with early-onset rickets, hypocalcemic seizures, and poor response to conventional therapy, particularly in the presence of consanguinity or sibling involvement. Early diagnosis and targeted calcitriol treatment result in excellent clinical and functional outcomes, underscoring the importance of maintaining a high index of suspicion and pursuing timely genetic confirmation.

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