CASE REPORT

Vitamin D-dependent rickets: a resurgence of the rachitic lung in the 21st century

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SUMMARY

Respiratory complications of rickets may be life-threatening particularly in developing countries. A 7-month-old boy presented with recurrent infections, seizures, failure to thrive, wheezing and respiratory distress progressing to global respiratory failure. Several antimicrobial regimens, bronchodilators and corticosteroids resulted in only short-term improvement. He was transferred from Cape Verde to a third-care hospital in Portugal. He was hypotonic and undernourished, with respiratory anguish and classical skeletal signs of rickets, despite vitamin D supplementation. Hypocalcaemia, normal phosphate levels and normal vitamin D status 25(OH)D₃ and 1.25(OH)₂D₃ pointed to vitamin D-dependent rickets type II. Treatment with high doses of calcium and calcitriol allowed progressive respiratory, musculoskeletal and neurological recovery. Although respiratory manifestations of rickets were described many years ago, the present case raises relevant issues about the level of diagnostic support, the risk of complications and how they should be assessed and monitored.

BACKGROUND

Vitamin D plays an important role in extraskeletal health (cardiovascular regulation processes, growth, cellular differentiation, oncogenesis prevention and modulation of immune response), besides calcium-phosphorus homeostasis and bone metabolism regulation.¹ Physiological concentrations of the active form, 1.25(OH)₂D₃ (calcitriol), has been shown to induce the human cathelicidin microbial peptide responsible for macroautophagy and subsequent killing of infectious agents including *Mycobacterium tuberculosis* and HIV1.² This activated form of vitamin D plays a simultaneous role in regulating inflammatory responses by inhibiting lymphocyte proliferation and activation, differentiation and survival of dendritic cells.¹

The 'rachitic lung' was described in the 60s and 70s of the last century, and was associated with nutritional deficiency, particularly in premature infants.^{3,4} In recent years, anecdotal reports of cases of chronic lung disease related to rickets were mainly due to vitamin D dietary deficiency associated with darker skin pigmentation, reduced solar exposure and exclusive breast feeding.^{5,6} In developed countries, respiratory symptoms associated with vitamin D deficiency are rarely described or are a consequence of iatrogenesis or genetic defects.

Despite these descriptions, cases of rickets with severe compromise of organs not directly involved

in the metabolic processes, such as chronic lung disease, are now rare.

We present a case of late diagnosis of vitamin D-resistant rickets that raises relevant issues about the level of diagnostic support, the risk of complications, and how such cases should be assessed and monitored.

CASE PRESENTATION

A 7-month-old African boy was admitted to Hospital Agostinho Neto, Cape-Verde, with fever, wheezing, shortness of breath and hypoxaemia. Family history was unremarkable and gestation uneventful. He had been admitted to hospital monthly, from the age of 3 months, for bronchiolitis, gastroenteritis, failure to thrive, seizures and pneumonia associated with oral candidiasis.

No aetiological agent for infections was found; tests were negative for *Toxoplasma gondii*, rubella, cytomegalovirus, *Plasmodium*, and HIV1 and 2, as was a Venereal Disease Research Laboratory (VDRL) test. Several empiric wide-spectrum antimicrobial regimens resulted in short-term improvement, response to bronchodilators and corticosteroids was insubstantial, and respiratory distress progressed uneventfully to global respiratory failure, requiring long-term oxygen therapy. Despite the absence of epidemiological or laboratory evidence for tuberculosis, the patient was started on triple tuberculosis medication, without improvement.

Owing to the clinical and radiographic evidence of rickets, calcium and cholecalciferol supplementation (1334UI 3id) was initiated. Cardiac examination was normal. The baby failed to thrive despite a well-tolerated high caloric ingestion of 195 mL/kg/day. He presented developmental delay; he was hypotonic, unable to sit and had poor vocalisations, but he did stare, and could visually follow objects and recognise familiar faces; additionally, he could transfer objects, exhibited a pincer grasp and explored objects orally.

At 10 months of age, he was transferred to Santa Maria Hospital, Portugal. On admission, he presented tachypnoea (80–90 cpm), hypoxaemia (SpO₂ < 93%, FiO₂ 0.4), severe chest retractions, nasal flaring, an expiratory moan, and an insistent cough accompanied by desaturation and tachycardia. Prolonged expiratory time and bilateral crackles were heard. He presented a bell-shaped thorax, wide anterior fontanelle and frontal bossing.

He had dark curly hair with no apparent anomalies. Episodic tremor of the superior right limb, preserving intentional movement, was identical to previously interpreted seizures. Small cervical,

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axillar and inguinal lymphadenopathies were palpable. He had significant growth compromise (weight as P50 for 1.5 months and length as P50 for 4 months for Center for Disease Control and Prevention scales).

INVESTIGATIONS

Laboratory tests revealed iron-deficiency anaemia with haemoglobin 10.1 g/dL (11.1–14.1 g/dL), no inflammatory pattern and normal renal function.

Basic screening for primary (lymphocyte subpopulations, immunoglobulins, CH50, total IgE) and acquired immunodeficiency (serological tests for HIV1/2) was negative.

Non-serotyped *Haemophilus influenzae* and extended-spectrum- β -lactamase-producing *Klebsiella pneumoniae* multiresistant (sensitive only to carbapenems) were isolated in initial sputum cultures and the boy was treated with meropenem, co-trimoxazole and azithromycin for 10 days. Subsequent cultures of bronchial specimens, blood, urine and gastric aspirate were negative including for acid-fast bacilli.

Tests for cystic fibrosis were negative and so was the 24 h pH monitoring for gastro-oesophageal reflux.

Thorax CT scan showed a bell-shaped thorax, diminished pulmonary complacency, prominent chondrocostal junctions, coarse bone trabeculation and pathological rib fractures, ground-glass opacities and atelectasis of the lung parenchyma, and absence of bronchiectasis and of mediastinal lymphadenopathies (figure 1).

Bone radiographs confirmed widening and fraying metaphyseal regions of the long bones, mainly in the proximal humerus; radius and ulna old fractures and incipient dorsolumbar scoliosis (figure 2).

Further investigation of phosphorus–calcium metabolism revealed hypocalcaemia (serum calcium 7.9 mg/dL (9–11), ionised calcium 0.86 mmol/L (1.13–1.32)), normal phosphate levels, parathyroid hormone 409.6 pg/mL (14–72), alkaline phosphatase 1673 U/L (<462), high urinary phosphate (144 mg/dL) and diminished phosphate tubular reabsorption (64.4%). Vitamin D status, both 25(OH)D₃ and 1.25(OH)₂D₃ revealed no deficits (with 25(OH)D₃ supplementation 1800 UI/day). Evaluation of teeth revealed no abnormalities.

A geneticist examination identified no dimorphism or syndromic disease. CYP27B1 and vitamin D receptor (VDR) gene sequencing revealed no mutations known to cause disease.

EEGs were normal.

Figure 1 Thorax CT scan of the patient at 11 months of age: compromise of thorax expansibility and diffuse abnormal density and coarse trabeculation of the bone. (1) Enlarged costochondral junctions ('rachitic rosary') and (2) Pathological rib fractures.

TREATMENT

The infant was initiated on calcium gluconate 10% (4 mL three times per day, approximately 110 mg Ca/day) and calcium carbonate 1 g/d (approximately 400 mg Ca/day), 25(OH)D₃ (maximum 3600 UI/day) and 1.25(OH)₂D₃ (progressively increased to 0.5 µg/day). Treatment was adjusted according to clinical evolution and laboratorial results with withdrawal of 25(OH)D₃ and maintenance of 1.25(OH)₂D₃ 0.25 µg/day (6 days/week). Tuberculosis medication was stopped soon after arrival and broad-spectrum antibiotics adjusted to the antimicrobial tests from cultures. Bronchodilator and steroids were discontinued and reinitiated only on exacerbations; a gradual decline in oxygen demand to 1 L/min by nasal cannula was noticed. Sodium valproate was stopped.

OUTCOME AND FOLLOW-UP

Skeletal (figures 3A–D) and thoracic deformation gradually improved, so did the respiratory distress, allowing withdrawal from oxygen after 9 months (the baby was 18 months of age). The baby was discharged at 15 months of age and re-evaluated in outpatient. There was a significant progress in growth (at 19 months his weight corresponded to P50 for 14 months and length to P50 for 6 months) and a notable tonus recovery was seen with achievement of important motor milestones, such as the ability to walk independently by 18 months.

DISCUSSION

The child's severe lung disease demanded evaluation for chronic lung diseases including cystic fibrosis, tuberculosis and immunodeficiency or lung disease secondary to gastro-oesophageal reflux. All of these were discarded.

Clinical, radiological and laboratory findings were diagnostic for hypocalcaemic rickets. This condition could be secondary to

Figure 2 Thorax radiograph of the patient at 10 months of age showing a bell-shaped thorax. (1) Areas of consolidation and atelectasis. (2) Widening, loss of definition and fraying of metaphysis. (3) Enlarged costochondral junctions with a beading aspect ('rachitic rosary') and (4) Healing fractures.

Figure 3 (A) and (C): Radiographic skeletal signs of rickets at 11 months of age. (1) Widening, loss of definition, cupping and fraying of metaphysis. (B) and (D): Skeletal radiographs of the patient at 15 months of age, evidencing signs of recovery with instituted therapy. (2) Persistence of widening of metaphysis, but recovery of its definition and (3) Signs of periosteal reaction evidencing signs of new bone deposition.

nutritional deficiency and could explain the hypocalcaemic seizures this child presented in the first year of life, and the delayed achievement of motor milestones due to decreased muscle tone and recurrent infection.^{7 8} Despite having several risk factors for nutritional vitamin D deficiency (late preterm, dark skin, low sun exposure due to multiple hospital admissions⁶), normal-high serum $1.25(\text{OH})_2\text{D}_3$ suggests a genetic aetiology: vitamin D-dependent rickets type I or II, both autosomal recessive disorders. Vitamin D-dependent rickets type I is caused by inactivating mutations in the *CYP27B1* gene (which encodes the enzyme 1α -hydroxylase), resulting in deficient conversion of $25(\text{OH})\text{D}_3$ to the active form $1.25(\text{OH})_2\text{D}_3$; type II is caused by mutations in the *VDR*, resulting in end-organ resistance to vitamin D action.

As this boy was under $25(\text{OH})\text{D}_3$, that could not be withheld to measure basal serum levels of $1.25(\text{OH})_2\text{D}_3$, interpretation of laboratory results and the distinction between these two forms

of vitamin D-dependent rickets turned particularly difficult. Furthermore, genetic tests did not identify mutations in *VDR* and *CYP27B1* genes that could account for this phenotype.

The absence of $1.25(\text{OH})_2\text{D}_3$ deficit under supplementation with $25(\text{OH})\text{D}_3$ 1800 IU/day (indicating that the conversion of $25(\text{OH})\text{D}_3$ to the active form $1.25(\text{OH})_2\text{D}_3$ was not completely compromised), and the patient's clinical and laboratory evolution, requiring supplementation at very high doses of calcium and calcitriol, suggested vitamin D-dependent rickets type II. However, alopecia (present in about two-thirds of patients with vitamin D-dependent rickets type II) was not present.⁹ Moreover, considering the patient's remarkable recovery under treatment with relatively small doses of calcitriol ($0.5 \mu\text{g}/\text{day}$), as opposed to the very high doses (up to $30\text{--}60 \mu\text{g}/\text{day}$) sometimes required to treat vitamin D-dependent rickets type II, vitamin D-dependent rickets type I could not be categorically excluded.

Adequate correction of phosphorus–calcium metabolism resulted in improvement of respiratory, musculoskeletal, neurological and growth recovery and infection control, indicating rickets as the origin of these multisystem manifestations.

This case is an important reminder that—in addition to the skeletal manifestations—anaemia, hypotonia, increased risk of infectious diseases, hypocalcaemic seizures and respiratory distress can all be associated with rickets.⁶ Decreased muscle tone and recurrent infections contribute to the delayed achievement of motor milestones. Anaemia may result from recurrent infections, associated nutritional deficits and myelofibrosis derived from vitamin D deficiency.¹⁰

The aetiology of respiratory disease in the context of rickets has been classically attributed to osteodystrophy of the thoracic cage, compression of lung parenchyma, and hypocalcaemic myopathy of the diaphragm and intercostal muscles, leading to impaired clearance and respiratory infections.¹¹ However, recent findings suggest that vitamin D's immune-regulatory effects are also important contributors.¹²

Vitamin D deficiency is re-emerging in several parts of the globe, including in Europe and the USA; a problem possibly aggravated by trends for so called 'natural' diets and lifestyles.¹³

By enabling rapid sequencing of large stretches of DNA base pairs spanning the entire exome or targeting a panel of genes of

interest, next-generation sequencing technology may provide the answers that current genetic tests could not. However, currently, in our practice, this innovative technology is still expensive and reserved only for circumstances in which the result could offer a practical benefit for the patient.

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Contributors ASCF was responsible for acquiring the information, drafting of the manuscript and subsequent revision, with help from all the coauthors. SL was responsible for the initial and current care of the patient in his home country. ARS and CS were responsible for the nephrological investigation and follow-up. LL was responsible for the imaging studies, and their interpretation and selection. LL, ARS, CS and TB provided clinical input into the article. TB was responsible for the original idea, final approval of the manuscript and respiratory follow-up of the patient.

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Learning points

- ▶ Neither is rickets in children from tropical countries always nutritional, nor is nutritional rickets extinct in developed countries.
- ▶ In addition to classical skeletal signs, hypocalcaemic rickets may present with extraskeletal signs, including respiratory distress and failure, anaemia, decreased muscle tone, delay in achievement of motor milestones, recurrent infections and hypocalcaemic seizures.
- ▶ Next-generation sequencing is a promising technology in cases of disease of genetic aetiology in which classical genetic tests are unable to identify the mutations responsible for disease.

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