

Nutritional Rickets in Ichthyosis and Response to Calcipotriene

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ABSTRACT. Nutritional rickets has occasionally been described in children with lamellar ichthyosis, but their vitamin D endocrine status has not been described. We report 3 cases of vitamin D-deficiency rickets associated with ichthyosis in African children.

A 13-month-old Nigerian boy with lamellar ichthyosis had rib beading, elevated alkaline phosphatase, and rachitic changes on radiographs. His rickets did not resolve with calcium therapy, and his 25-hydroxyvitamin D level was low. His rickets resolved with parenteral vitamin D treatment, but his skin did not improve. Topical 0.005% calcipotriene (an analog of 1,25-dihydroxyvitamin D that has been useful in treating adults with psoriasis) was similarly ineffective in improving the child's skin condition.

An 8-year-old Nigerian boy with life-long skin findings consistent with lamellar ichthyosis had windswept deformity of the legs with rib beading and enlargement of the wrists and ankles. Radiographs showed active rickets, and the boy had an elevated alkaline phosphatase level and a decreased calcium level. Before knowing that his 25-hydroxyvitamin D level was low, he was treated with calcium and showed radiologic improvement. The skin did not improve with resolution of the rickets but did improve with unilateral topical application of 0.005% calcipotriene.

A 7-year-old South African girl presented with progressive windswept deformities of the legs and a 4-year history of skin disease (and a skin biopsy consistent with X-linked ichthyosis). Radiographs and biochemical data confirmed active rickets. Her rickets improved dramatically with vitamin D treatment.

Thus, 3 African children with ichthyosis developed vitamin D-deficiency rickets, probably because of a combination of impaired skin production and sunlight avoidance. This is consistent with previous findings of hypovitaminosis D in adults with ichthyosis and other disorders of keratinization. Measurement of 25-hydroxyvitamin D may be indicated in children with ichthyosis to identify those at risk for vitamin D-deficiency rickets, because it is possible that the cutaneous synthesis of vitamin D in such children is impaired.

Although the ichthyosis did not improve with resolution of vitamin D deficiency and rickets, 1 of 2 children treated with topical calcipotriene showed improvement in the treated areas of skin. Calcipotriene does not seem to be effective in reversing systemic vitamin D deficiency but can be effective in improving the severity of skin disease in children with ichthyosis. *Pediatrics* 2004; 114:e119–e123. URL: <http://www.pediatrics.org/cgi/content/full/114/1/e119>; bone, skin, children, vitamin D deficiency, calcium, ichthyosis rickets.

Vitamin D fortification of milk and other foods has nearly eliminated vitamin D-deficiency rickets from industrialized nations. In the developing world, however, nutritional rickets is still a common disease that may result from deficiency of either calcium or vitamin D.^{1–3} Nutritional rickets has occasionally been described in association with lamellar ichthyosis,^{4–6} but the vitamin D status was not reported. We describe 2 Nigerian children with lamellar ichthyosis and a third South African child with presumed X-linked ichthyosis associated with nutritional rickets and report on the response of 2 children to topical calcipotriene, a vitamin D analog.

CASE REPORTS

Case 1

During a dietary rickets-prevention trial in Jos, Nigeria, a 13-month-old boy was identified with rickets by radiographic screening. Beading of the costochondral junctions was palpable, but no wrist enlargement or long-bone deformity was evident. Radiographs of the wrists and knees showed marked fraying and cupping of the distal metaphyses consistent with rickets. The mother reported that the child had had “dry skin” since birth. None of the child's 4 older siblings or parents had any history of bone or skin disease; however, a sister, born 2 years after this child was first seen, had an identical skin disease. No factors, including sunlight, seemed to aggravate scaling of the skin. The child's estimated average sunlight exposure was ~1 hour daily. Anthropometric data (Table 1) showed stunted growth without wasting. Generalized polygonal scales were more prominent on the extremities than the trunk or face (Fig 1). Hyperkeratosis of the palms and soles was present, but no ectropion was evident.

The child was initially treated with calcium (800 mg daily), because most Nigerian children with rickets do not have vitamin D deficiency and respond well to calcium alone.³ However, his bones failed to heal radiographically during 6 months of calcium treatment. Serum from his initial evaluation had been stored at –20°C and was transported on dry ice to the Mayo Clinic. Biochemical results (Table 1) indicated a low 25-hydroxyvitamin D concentration, consistent with vitamin D deficiency. His rickets, as documented radiographically, healed rapidly within 3 months after administration of vitamin D₃ (600 000 U intramuscularly), but the scaling of his skin did not change.

Whitfield ointment (benzoic acid 6%/salicylic acid 3%) produced only minimal softening of skin scales. Skin biopsy showed orthohyperkeratosis and increased granular layer thickness. After informed consent and after the rickets had resolved with paren-

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Received for publication Oct 20, 2003; accepted Feb 17, 2004.

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TABLE 1. Anthropometric and Laboratory Features of Rachitic Subjects With Ichthyosis

Characteristic	Case 1	Case 2	Case 3	Reference Range
Anthropometric data				
Weight, kg	6.7	15.3	24.4	
Height, cm	62.8	93.5	115	
Weight for height, Z score	0.32	0.82	1.98	
Weight for age, Z score	-3.5	-3.1	0.42	
Height for age, Z score	-5	-6	-1.3	
Serum*				
Calcium, mg/dL				9.6-10.6
Pretreatment	8.9	6.9	6.8	
Posttreatment		9.0	9.6	
Corrected calcium, mg/dL†	8.5	5.7	7.4	9.6-10.6
Phosphorus, mg/dL	2.0	3.9	3.0	4.3-5.4
Alkaline phosphatase, U/L				<400
Pretreatment	707	3491	987	
Posttreatment			333	
Albumin, g/dL	4.3	5.0	3.6	3.5-5.0
25-Hydroxyvitamin D, ng/mL				8-38
Pretreatment	<4.5	<4.5		
Posttreatment	60	10		
1,25-Dihydroxyvitamin D, pg/mL				22-67
Pretreatment	57	102	110	
Posttreatment	200	139		
Parathyroid hormone, pg/mL				1.0-5.2
Pretreatment	63	39	173	
Posttreatment	4.2	22	31	
Urinary calcium excretion, mg/d		0.52	12.5	25-300
Fractional absorption of calcium, %‡		76		15-60

* To convert values for calcium to millimoles per liter, multiply by 0.25; to convert values for phosphorus to millimoles per liter, multiply by 0.32; to convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50; to convert values for 1,25-dihydroxyvitamin D to picomoles per liter, multiply by 2.40; and to convert the values for parathyroid hormone to picomoles per liter, multiply by 0.11.

† Serum calcium was corrected for albumin concentration by using the following formula: corrected calcium (mg/dL) = total calcium (mg/dL) + 1.2 × [4 - albumin (g/dL)].

‡ As determined by 24-hour collection of urine after oral administration of Ca⁴⁵ and intravenous administration of Ca⁴⁷.

teral vitamin D treatment, the mother was instructed to apply calcipotriene ointment 0.005% (Dovonex, Bristol-Myers Squibb; 30 g weekly) on only the right side of the body, excluding the face and genital area, and petrolatum to the left side of the body. After 6 weeks of topical treatment, with compliance documented by the return of empty calcipotriene tubes, no difference between the right and left sides was observed.

Case 2

An 8-year-old Nigerian boy presented with windswept deformity of the legs and pain with walking. He also had scaling of the skin that had been present since birth. His father reported that the child avoided sunlight, because it produced "heat" in the face. There was no family history of a similar skin disease, but the child's mother and father shared common great-grandparents. The child had short stature without wasting (Table 1). Examination showed generalized polygonal scales, bilateral ectropion (Fig 2), and enlargement of the costochondral junctions, wrists, and ankles. Hyperkeratosis of the palms and soles was absent during the rainy season, but it appeared during the dry season. Radiographs of the wrists and knees confirmed active rickets (Fig 3).

Laboratory findings are shown in Table 1. Initial treatment with calcium was initiated before all laboratory data were available. Because his calcium absorption (determined as part of an ongoing investigation using oral and intravenous administration of stable calcium isotopes) was high despite a low concentration of 25-hydroxyvitamin D, treatment with elemental calcium (1000 mg daily) was continued, as was counsel to increase exposure to sunlight. Radiographic improvement was noted at 6 months despite 50% compliance by pill counts. The ichthyosis did not improve with calcium, Whitfield ointment, or 12% lactic acid cream.

Skin biopsy showed orthohyperkeratosis and increased granular layer thickness. After 6 months of calcium treatment when radiologic improvement had been documented and after informed consent, the father was instructed to apply calcipotriene ointment

0.005% (Dovonex; 30 g weekly) on only the right side of the child's body, excluding the face and genital area, and petrolatum on the left side. After 6 weeks, softening of the skin and desquamation was evident on the treated side, and additional improvement was noted after 12 weeks (Fig 4). The trunk demonstrated greater improvement than the distal extremities. Serum calcium remained in the normal range (9.0 mg/dL).

Case 3

A 7-year-old South African girl presented with progressive windswept deformity of the legs and scaling of the skin since 4 years of age. Her mother reported that the child was active and playing in sunlight. There was no family history of a similar skin or bone disease. Examination showed generalized epidermolytic hyperkeratosis, particularly on the face. Despite the deformities of the lower limbs, there was neither wrist enlargement nor costochondral enlargement. Radiographs of the wrists and knees confirmed active rickets.

Laboratory findings are shown in Table 1. The elevated alkaline phosphatase level suggested active rickets, and the low calcium, low phosphate, and high parathyroid hormone were consistent with that diagnosis. Skin biopsy showed marked hyperkeratosis with a clearly defined granular layer. There was no parakeratosis and no hyperkeratosis of follicles and sweat gland ducts. The underlying dermis showed scanty perivascular lymphoid infiltrates. These features were felt to be most consistent with X-linked ichthyosis. Her rickets was treated with oral vitamin D (5000 IU daily), and her ichthyosis was treated concurrently with 10% urea in aqueous cream as an ointment and white soft paraffin. Biochemical improvement was noted within 3 months, and radiologic healing occurred within 6 months. The ichthyosis also improved, although she had pruritis during the dry season. Her trunk demonstrated greater improvement than her extremities and face.

Fig 1. Polygonal scales characteristic of lamellar ichthyosis (case 1).



Fig 2. Polygonal scales and ectropion in a 7-year-old child with lamellar ichthyosis (case 2).

DISCUSSION

We have described the vitamin D endocrine status of 2 Nigerian children and 1 South African child with ichthyosis (2 with lamellar ichthyosis and 1 with possible X-linked ichthyosis) and nutritional rickets. Restoration of their biochemical abnormalities toward normal and healing of their rickets did not improve the ichthyosis. The skin of 1 child moderately improved during treatment with topical calcipotriene, and that of another child improved moderately with an emulsifying ointment.

The primary question arising from these case reports is whether ichthyosis and rickets are causally related or simply coincidental. Are children with ichthyosis at greater risk of vitamin D deficiency? Vitamin D-deficiency rickets results from inadequate sunlight exposure and intake of dietary vitamin D. Two of the children described had undetectable concentrations of 25-hydroxyvitamin D, indicating defi-

ciency of vitamin D, and the third child responded promptly to vitamin D supplements. Because of associated facial discomfort, the oldest child avoided sunlight, which may have contributed to vitamin D deficiency. Unexpectedly, despite vitamin D deficiency, calcium absorption was greater than normal in the 1 child in which it was measured, and the concentration of hormonally active 1,25-dihydroxyvitamin D was elevated in 2 of the 3 children.

In a study of 41 Sudanese children with rickets attributed to vitamin D deficiency, 3 were reported to have ichthyosis, but values of vitamin D metabolites were not described.⁴ In another report, clinical features of rickets were described in a child with 5 other male family members with ichthyosis vulgaris,⁵ but vitamin D metabolites were not measured. Two other reports of children with ichthyosis and nutritional rickets also did not describe vitamin D metabolite values, but rickets healed with vitamin D and

Fig 3. Radiograph of wrist demonstrating longitudinal widening of epiphyseal plates and fraying of distal metaphyses of the radius and ulna characteristic of rickets (case 2).



Fig 4. Response to calcipotriene in lamellar ichthyosis. The right arm was treated with topical calcipotriene for 12 weeks, whereas the left arm was treated only with petrolatum. There is reduced scaling and roughness on the treated side (case 2).

calcium.^{6,7} The children presented here apparently developed vitamin D-deficiency rickets due to a combination of impaired skin production and sunlight avoidance.

Generalized disorders of keratinization may predispose children to vitamin D-deficiency rickets. Milstone et al⁸ reported elevated parathyroid hormone and low-to-normal 25-hydroxyvitamin D values in patients with various disorders of keratinization, including 3 adult patients with lamellar ichthyosis. Milstone et al postulated that defective vitamin D synthesis in the diseased epidermis, avoidance of sunlight, or excessive loss of calcium through the skin could stimulate parathyroid hormone secretion. Any of these mechanisms could put children with ichthyosis at risk for rickets. In a subsequent study, however, subjects with elevated parathyroid hormone values did not have significantly lower 25-

hydroxyvitamin D values than those with normal parathyroid hormone values.⁹

Despite healing of rickets and restoration of endocrine abnormalities toward normal in our patients, the skin disease did not improve after treatment with calcium or intramuscular vitamin D (cholecalciferol). This is consistent with the reported ineffectiveness of oral 1 α -hydroxyvitamin D₃ in ichthyosis.¹⁰ Topical calcipotriene (calcipotriol), which suppresses proliferation and stimulates terminal differentiation of epidermal keratinocytes and has been used to treat psoriasis in adults, restored the skin to a more normal texture in 1 of the 2 patients. Hypercalcemia did not occur in either child. The generally low calcium content of the Nigerian diet may have protected them from hypercalcemia. Topical calcipotriene in quantities of up to 120 g weekly in adults has been reported to reduce scaling and roughness in lamellar ichthy-

osis without increasing serum calcium.¹¹ The relatively low dose of calcipotriene we used may account for the failure of 1 of the patients to respond.

Conversely, one could speculate that the topical application of the vitamin D analog could have helped correct the systemic vitamin D deficiency. Approximately 5% of the topically applied calcipotriene is thought to be absorbed systemically. In fact, however, calcipotriene is an analog of 1,25-dihydroxyvitamin D. As such, it would not be expected to alter the levels of the precursor, 25-hydroxyvitamin D. In our first case, calcipotriene was applied after vitamin D had been replenished parenterally. In the second case, the vitamin D level remained low even after calcipotriene was used. Thus, it does not seem that calcipotriene has a significant influence on systemic vitamin D deficiency.

Additional studies to determine if epidermal production of vitamin D is reduced in ichthyosis would clarify whether this factor could be responsible for an association with nutritional rickets. Whether topical calcipotriene is sufficient to prevent vitamin D deficiency is also worthy of future study. Meanwhile, it may be prudent to measure 25-hydroxyvitamin D in children with ichthyosis and to provide vitamin D supplementation to those with low concentrations of 25-hydroxyvitamin D who may be at risk for nutritional rickets, particularly in settings of limited dietary calcium and/or sunlight exposure.

ACKNOWLEDGMENTS

This work was supported in part by a grant from the Thrasher Research Fund (Salt Lake City, UT).

We are grateful to Dr Steve Abrams for determination of the fractional calcium absorption; Dr Denis Benjamin for processing and interpreting the histopathologic skin specimens; and Dr Deb Basu for care of one of the subjects.

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DOI: 10.1542/peds.114.1.e119

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