Unusual association of diseases/symptoms

Lamellar ichthyosis with genu valgum: unfolding the link

Nilakshi Deka, Dipti Sarma, Uma Kaimal Saikia

Department of Endocrinology, Gauhati Medical College, Guwahati, India

Correspondence to Dr Nilakshi Deka, nilsdeka@yahoo.co.in

Summary

We describe a case of lamellar ichthyosis with bilateral genu valgum. The association of genu valgum with congenital ichthyosis is rare. Our patient, a 22-year-old girl, had lamellar ichthyosis and was born with a collodion membrane. She developed progressive valgus deformity of the knees of 5 years duration associated with difficulty in walking. On evaluation, she had generalised scaly skin lesions along with bilateral genu valgum and biochemical evidence of vitamin D deficiency. Skin serves as an important site for vitamin D synthesis and thus skeletal deformities secondary to vitamin D deficiency may occur in cases of congenital ichthyosis, causing a diagnostic dilemma due to the unusual association. This case serves as a reminder that clinicians need to be aware of such an association in order to prevent, appropriately diagnose and adequately treat the rare case of congenital ichthyosis with rickets and osteomalacia.

BACKGROUND

Vitamin D, the so-called sunshine vitamin is essential for calcium metabolism and optimal skeletal health. In humans, a sizeable proportion of vitamin D requirements are met by synthesis in the skin from 7-dehydrocholesterol in the presence of ultraviolet B radiation between the wavelengths 290 and 315 nm. Dietary sources like fatty fish, egg yolks, plants and grains also help to meet the vitamin D requirements. However since most foods (with the exception of fatty fish) contain only small amounts of vitamin D₃, individuals must rely on either adequate sunlight exposure or dietary supplements for an adequate supply of vitamin D.¹ Vitamin D deficiency may thus result from chronic skin disorders limiting vitamin D synthesis in skin.

Lamellar ichthyosis is a chronic and disfiguring disease which has a tremendous impact on family and social life. It is an autosomal-recessive disorder that is apparent at birth and is present throughout life. An autosomal-dominant pattern of inheritance of lamellar ichthyosis has also been described. Prevalence is less than 1 case per 300 000 individuals.² The association of rickets or osteomalacia with ichthyosis is rare though there are reports of vitamin D deficiency and secondary hyperparathyroidism in patients of various disorders of keratinisation.² We present the following case of genu valgum with lamellar ichthyosis for its rarity.

CASE PRESENTATION

A 22-year-old girl, presented to us with a history of progressive knee deformity and difficulty in walking of 5 years duration. She was born of consanguineous marriage at term by normal vaginal delivery, third in birth order with two normal sibs. She was noticed to have collodion membrane at birth which was shed within 48 h to be followed by generalised erythema and fish-like scaly skin lesions which persisted in the subsequent years. She was also noticed to have a negligible sweating from childhood. She was immunised appropriately and

developmental milestones were normal. She was average in scholastic performances but dropped out from school in the 9th standard due to social disfigurement and used to stay mostly indoors limiting average daily sun exposure to around 15 min during winter and almost negligible during summer. Her menstrual history was normal. Since 17 years of age she started having pain in both the knees with difficulty in walking, climbing stairs and rising up from squatting position. Gradually she noticed valgus deformity of the knees involving initially the right and then the left within a period of 6 months. She also complained of mild burning sensation and grittiness of her eyes since 14 years of age associated with mild difficulty in hearing and right ear discharge. There was no history of trauma to the knees, fractures, chronic diarrhoea or steatorrhoea suggestive of malabsorption or any history of renal disorder. Dietary history revealed adequate intake of foods rich in calcium and vitamin D. There was no family history of similarly affected individuals. Treatment history included various topical applications like glycerine and urea cream since childhood and intermittent oral retinoid therapy for the past 3 years.

Examination revealed a height of 153 cm (25th–50th percentile), weight of 40 kg, (5th–10th percentile), body mass index of 17.09, upper segment:lower segment ratio of 1.23 and an arm span of 153 cm. Mid-parental target height was 156 cm. Large fine grey scales were seen mostly on trunk and limbs with minimal involvement of face and sparing of palms and soles (figure 1). Dandruff was present and mucosal surfaces and teeth were normal. She had bilateral madarosis on lateral aspects. There was bilateral genu valgum with intermalleolar distance of 7.5 inches (figure 2A). Routine investigations including serum creatinine and blood gas analysis were normal. Serum thyroid stimulating hormone was 2.17 µIU/ml, serum calcium: 8.8 (8.5–10.2) mg/dl, serum phosphorus: 3.2 (2.5–4.5) mg/dl, serum albumin: 4.1 gm/dl, serum alkaline phosphatase: 485 (38–126) U/l, 25-hydroxy-vitamin D: 9.12 ng/ml (deficiency <20 ng/ml), serum parathyroid

Figure 1 Lamellar ichthyosis. Typical plate like scaly skin lesions.

hormone (PTH): 68.8 (14–72) pg/ml. Radiographs showed valgus deformity of both knees (figure 2B) with thinned out cortex. A dexta scan was done which revealed a T score of –2.1 at the lumbar spine suggestive of osteopenia and a T score of –0.8 at the hip. Skin biopsy revealed mild-to-moderate epidermal acanthosis with a well-formed, focally thickened granular layer and thick laminated bright pink ‘ichthyotic’ stratum corneum, features consistent with lamellar ichthyosis (figure 3). Ophthalmological evaluation revealed superficial punctuate keratitis bilaterally (figure 4). She was also found to have chronic suppurative otitis media bilaterally with central perforation on right. Pure tone audiometry revealed bilateral conductive hearing loss. Dermatology opinion was taken and she was started on oral retinoids and topical emollients.

On the basis of clinical and laboratory evaluation, a diagnosis of lamellar ichthyosis with genu valgum due to vitamin D deficiency was made. Vitamin D deficiency was deemed to be consequent to inadequate synthesis in the skin. She was treated with oral cholecalciferol 60 000 IU once weekly for 8 weeks following which serum 25(OH) vit D increased to 32.8 ng/ml. Clinically, a marked improvement in symptoms like pain in thighs and knees was noted along with resolution of difficulty in walking, climbing stairs and getting up from squatting posture. She was thereafter maintained on a dose of 60 000 IU orally once a month in view of chronicity of her skin problem. She was also referred to the orthopaedics department for corrective osteotomy. On follow-up her skin lesion showed mild improvement and no further bony deformities were noted.

INVESTIGATIONS

Parameter	Patient's value	Reference value
Serum calcium (mg/dl)	8.8	8.5–10.2
Serum phosphorus (mg/dl)	3.2	2.5–4.5
Serum alkaline phosphatase (U/l)	485	38–126
Serum albumin (gm/dl)	4.1	3.7–4.9
24 h urinary calcium (mg/24 h)	120	100–249
25-Hydroxy-vitamin D (ng/ml)	9.12	Deficiency <20
Serum parathyroid hormone (pg/ml)	68.8	14–72
Arterial blood gas analysis: pH	7.39	7.35–7.45
Thyroid-stimulating hormone (μIU/ml)	2.17	0.4–4
Creatinine (mg/dl)	0.7	0.6–1.1
Dexta scan: T score	Spine: –2.1; hip: –0.8	<ul style="list-style-type: none"> • Normal bone: T score better than –1 • Osteopenia: T score between –1 and –2.5 • Osteoporosis: T score less than –2.5

TREATMENT

Oral cholecalciferol 60 000 IU once weekly for 8 weeks followed by a maintenance dose of 60 000 IU monthly in view of the chronic nature of her skin problem.

She was also referred to the orthopaedics department for corrective osteotomy.

OUTCOME AND FOLLOW-UP

On follow-up her skin lesions showed mild improvement along with relief of symptoms of pain in the lower limbs and proximal muscle weakness. Valgus deformity of the knees also improved following corrective osteotomy and no further bony deformities were noted.

DISCUSSION

Vitamin D has been recently catapulted to limelight with research studies linking vitamin D apart from bone health to an exhaustive list of diseases ranging from cancer, heart disease, multiple sclerosis, parkinsons disease, obesity, aging and falls to diabetes.³ The metabolic product of vitamin D is a potent, pleiotropic, repair and maintenance, secosteroid hormone that targets more than 200 human genes in a wide variety of tissues, meaning that it has as many mechanisms of action as genes it targets.⁴

In the presence of ultraviolet radiation between wavelengths of 290 and 315 nm, 7-dehydrocholesterol in the skin is converted to previtamin D₃ which is then converted to vitamin D₃ in the skin after a thermally induced isomerisation reaction. The newly synthesised vitamin D₃ then enters the circulation and is sequentially hydroxylated in the liver by vitamin D 25-hydroxylase and then in the kidney by the P 450 enzyme 25-hydroxy vitamin D-1 α hydroxylase. The enzyme 25 (OH) vitamin D 1α hydroxylase is highly regulated by the parathyroid hormone. The hydroxylation product 1, 25 (OH)₂D₃ also known as calcitriol enters the cell and acts via the vitamin D receptor which is a nuclear receptor, to increase the transcription of vitamin D-related genes. The major function of vitamin D is to increase the efficiency of calcium and phosphorus absorption from the intestine for proper mineralisation of the bones. The second major function is maturation of the

Figure 2 (A) Skeletal deformity – genu valgum. (B) x-Ray of the knees showing genu valgum on antero posterior view.

osteoclasts to resorb calcium from the bones.¹ Thus vitamin D and bone health are inseparable entities.

Childhood ichthyosis, a disorder of keratinisation may result in impaired synthesis of vitamin D and hence poor mineralisation of bones. Following mechanisms have been postulated: (1) defective vitamin D synthesis in the diseased epidermis, (2) increased keratinocyte proliferation resulting in poor or no penetration of skin by sunlight, (3) excessive loss of calcium through the diseased skin, (4) avoidance of sun exposure due to the disease and (5) systemic retinoids which decrease calcium absorption in the gut.⁵

Lamellar ichthyosis comes from the Latin word *lamella* meaning plate.² The newborn may be born encased in a collodion membrane that dries within hours and peels off within first few weeks of life. The shedding of the membrane reveals generalised scaling with variable redness of

Figure 4 Superficial punctate keratitis as seen on fluorescein staining.

Figure 3 Skin biopsy taken from back showing thick laminated bright pink 'ichthyotic' stratum corneum consistent with lamellar ichthyosis. (haematoxylin – eosin stain).

the skin. The scaling may be fine or platelike, resembling fish skin. Additional common features are ectropion, eclabion, superficial punctuate keratitis, loss of eyebrows and lashes. Patients with lamellar ichthyosis have accelerated epidermal turnover with proliferative hyperkeratosis. This involves a mutation in the gene for the enzyme transglutaminase 1 (*TGM1*) involved in the formation of the cornified cell envelope. The formation of the cornified cell envelope is an essential scaffold upon which normal intercellular lipid layer formation in the stratum corneum occurs. Mutations in the *TGM1* secondarily cause defects in the intercellular lipid layers in the stratum corneum, leading to defective barrier function of the stratum corneum and to the ichthyotic phenotype seen in lamellar ichthyosis. Genetic linkage studies performed on families with classic lamellar ichthyosis show markers on chromosome 14q11 containing the transglutaminase 1 gene.²

Although rare, there are reports of rickets associated with ichthyosiform dermatoses in the literature. In a series of 41 Sudanese children with rickets due to vitamin D deficiency, three had ichthyosis.⁶ Milstone *et al*⁵ in a series of 15 patients with various disorders of keratinisation, reported elevated parathyroid hormone and low-to-normal 25-hydroxyvitamin D values in five patients (bullous congenital ichthyosiform erythroderma (n=2), lamellar ichthyosis (n=1), pityriasis rubra pilaris (n=1) and ichthyosis linearis circumflexa (n=1)), possibly reflecting a secondary hyperparathyroidism. Ingen-Housz-Oro *et al*⁷ in a study of nine patients of European and North American descent with non-bullous congenital ichthyosis found marked 25-(OH)D deficiency, and it was more pronounced in the three patients from North America, perhaps because of the difference in skin pigmentation. Bone mineral density was measured in all patients and femoral neck osteodensitometry indicated values near the osteopenic threshold in two patients. Sethuram *et al*⁸ have described five children out of whom four children had lamellar ichthyosis and one child had non-bullous ichthyosiform erythroderma/psoriasis with atopy. All had biochemical and radiological evidence of rickets and two had very severe skeletal deformities. Bhagat *et al*⁹ have reported two cases of severe bilateral rachitic genu valgum in patients with non-bullous congenital ichthyosiform erythroderma.

In our patient a diagnosis of lamellar ichthyosis was confirmed on the basis of history, clinical features and histopathology. Serum vitamin D was found to be deficient along with the presence of bilateral genu valgum. Though serum PTH level was within range it was on the higher side of normal. There was no clinical or radiological evidence of rickets suggesting that genu valgum was secondary to osteomalacia as a result of vitamin D deficiency.

Several studies have demonstrated low serum 25(OH) vitamin D levels in populations across India despite abundant sunlight, which may be because of skin pigmentation and inadequate direct sunlight exposure.^{10–12} In India dairy products and food fats are not fortified with vitamin D, which, along with a low calcium and high phytate diet, is another contributing factor.^{11 13 14} In the presence of such a background prevalence of vitamin D

deficiency, a second insult like ichthyosis may tip off the delicate balance of vitamin D and bone mineral metabolism to result in rickets and osteomalacia.

Learning points

- The association of metabolic bone disease with chronic disorders of keratinisation is rare.
- Skin serves a major role in meeting the vitamin D requirements of our body and thus disorders of keratinisation can result in vitamin D deficiency with consequent crippling skeletal deformities.
- In any case of congenital ichthyosis, the possibility of vitamin D deficiency should be kept in mind. Early supplementation in cases of deficiency prevents rickets and osteomalacia.
- Patients with ichthyosis would also probably require lifelong vitamin D supplementation in view of chronicity of their skin lesions.

Competing interests None.

Patient consent Obtained.

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