Linear sebaceous naevus syndrome and resistant rickets

From the Hospital for Children, Great Ormond Street, London, England

The association between vitamin-D-resistant rickets and linear sebaceous naevus syndrome is extremely rare. Only eight cases have been described in the English literature and in none were the skeletal aspects addressed. We present three new cases and describe the musculoskeletal features. The details and outcome of surgery for correction of the deformities are discussed. The disturbances of metabolism of vitamin D and the effects of pharmacological treatment are also described.

Received 24 April 2002; Accepted after revision

Linear sebaceous naevus syndrome (LSNS), also known as epidermal naevus syndrome (ENS), is characterised by congenital anomalies affecting multiple systems in the body, including the skin, skeleton and central nervous system.1 The ‘sebaceous naevus’ was first recognised in 1895 when Jadasson described smooth, yellow or brown verrucous skin lesions, free from hair follicles, and distributed in a localised, linear, or generalised pattern.2 The naevi are symmetrical, tend to be more extensive on one side of the body and follow a morphological pattern of Blaschko’s lines.3 Involvement of the central nervous system is more common when skin lesions are on the mid-portion of the face.2 Precocious puberty is a rare associated finding.4 Sugarman and Reed5 were the first to report a patient with vitamin-D-resistant rickets in association with ENS. This is extremely rare and, to our knowledge, only eight cases have been described hitherto in the English literature.4,9 In none of these reports were the musculoskeletal features discussed.

We present three new patients in whom the musculoskeletal aspects and their management are addressed.

Case reports

All the patients had normal or nearly normal serum calcium levels, hypophosphataemia, elevated serum alkaline phosphatase, decreased renal tubular reabsorption of phosphorus, radiological evidence of rickets and a lack of response to normal therapeutic doses of vitamin D, thus confirming the diagnosis of hypophosphataemic vitamin-D-resistant rickets. The pre- and post-treatment biochemical profiles are summarised in Table I.

Case 1. A Caucasian boy was born with extensive epidermal naevi of his face and neck. There was no relevant family history. He started to limp at the age of two years and developed pathological fractures of the lower limbs. The diagnosis of phosphaturic rickets was made biochemically and he began treatment with phosphate and vitamin-D supplements. Between the ages of two and seven years, when he was referred to us, he had multiple fractures involving his right femur and tibia and could only mobilise by bottom shuffling. His right femur and both tibiae (Fig. 1) showed marked bowing associated with pathological fractures.

Further examination and investigations showed nephrocalcinosis, corneal calcification and mild aortic regurgitation associated with calcification of the aortic valve.

The skin lesions were treated by laser therapy. After correction of the metabolic parameters he underwent multiple osteotomies with rodding and bone grafting of the femur (Fig. 2) and osteotomies with rodding of both tibiae. Postoperatively, treatment with calcitriol and oral phosphate was continued. The osteotomies united unremarkably. He was mobilised on crutches at two weeks and was fully weight-bearing at three months when radiological union was demonstrable. The osteopenia improved with replacement therapy. He subsequently underwent epiphysiodesis of the distal femur and proximal tibia of the left leg for residual leg-length discrepancy.

Eight years after starting treatment, he is walking independently and continues with calcitriol and phosphate supplements.

Case 2. An Asian child born prematurely (32 weeks) of consanguineous parents presented at the age of six years.
having never stood or walked. There was no relevant family history. Examination showed a classical linear pattern of naevi (Fig. 3), predominantly unilateral, in an axial and appendicular distribution. He had been referred as a case of ‘disappearing bone disease’, but investigations (biochemical and radiological) showed characteristic findings of hypophosphataemic vitamin-D-resistant rickets. A skin biopsy was typical of epidermal naevus. There was severe bowing of the femora and tibiae (Figs 4 and 5) and a leg-length discrepancy of 8 cm.

Table 1. Summary of the metabolic and biochemical parameters before and after replacement therapy in the three patients with LSNS and vitamin-D-resistant rickets

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1</td>
<td>Case 2</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>8.9</td>
<td>8.8</td>
</tr>
<tr>
<td>(normal 9 to 11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>(normal 2.5 to 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum alkaline phosphatase (IU)</td>
<td>340</td>
<td>330</td>
</tr>
<tr>
<td>(normal 20 to 124)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular reabsorption of phosphorus (%)</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>(normal 85 to 95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-hydroxy-cholecalciferol (ng/ml)</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>(normal 15 to 80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25-dihydroxycholecalciferol (pg/ml)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>(normal 20 to 75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum parathyroid hormone (ng/ml)</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>(normal 0.4 to 1.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 2. Photograph showing the classical linear pattern of sebaceous naevi on the forearm, chest wall and base of neck.

Case 2. Clinical photograph showing deformities of the limbs.

Case 2. AP radiographs showing a) views of the pelvis with both femora and b) views of the knees with tibiae and ankles. They show severe osteopenia with bilateral coxa vara, pathological fractures and bowing deformities of the long bones, frayed, cupped metaphyses, widened zones of provisional calcification, and indistinct cortical margins especially of the metaphyses and epiphyses.

Case 2. Photograph showing that after replacement therapy the patient recovered muscle tone and improved bone density. He is able to walk with crutches and a shoe raise.
The epidermal naevi were treated by laser therapy. He was also started on replacement therapy with calcitriol and phosphates. Muscle tone and bone density improved remarkably and within six months he could stand with a walking frame and subsequently walked with crutches (Fig. 6).

The patient and his parents refused correction of the deformities and six years after presentation, he is still walking with crutches.

**Case 3.** An Afro-American boy was referred at the age of three years with inability to walk, skin lesions and multiple progressive deformities. There was no history of parental consanguinity. CT of the brain showed enlarged ventricles on the same side as his predominant skin lesions, although there was no evidence of mental retardation or neurological symptoms.

The skin lesions were mainly on the scalp, face, neck, arms, the sides of the chest, back and upper lateral thighs (Fig. 7). A skin biopsy confirmed sebaceous naevi. Early radiographs had shown little abnormality (Fig. 8) but later, when he presented to us, there were features of rickets and generalised osteopenia (Fig. 9). The biochemical results were consistent with hypophosphataemic rickets.

He had a mild kyphoscoliosis, extensive rachitic abnormalities of the wrists, knees and ankles and marked genu valgum on the right. There was severe bowing of the right femur and flexion contractures of both hips, measuring 30° on the left and 70° on the right. There were flexion deformities of the knee of 20° on the left and 40° on the right. There was a 20° fixed equinus deformity on the right side and the limb was 6 cm shorter than the left.

---

**Fig. 8**
Case 3. AP view of the pelvis with both femora in infancy showing almost normal radiological features.

**Fig. 9**
Case 3. AP view of the pelvis at presentation, when the patient was three years old. It shows severe osteopenia, bilateral coxa vara, and the changes associated with rickets.
The skin lesions were treated by laser therapy. He was started on oral replacement therapy, but could not tolerate this. He therefore underwent a gastrotomy, responding remarkably and becoming fit enough for correction of the deformity. Multiple osteotomies of the right femur with intramedullary rodding and soft-tissue release of the flexion deformity of the knee were followed three weeks later by a soft-tissue release of the hip. At operation the skin was noted to be thick and vascular, whereas the underlying soft tissues and periosteum seemed normal. The medullary canal was poorly defined or absent, but the bone quality was surprisingly good with excellent stability after rodding.

After operation, calcitriol and phosphate were continued. There were no problems with the healing of the osteotomies or surgical wounds. Muscle tone and motor development improved dramatically with medical treatment. At follow-up 1.5 years after treatment he is walking short distances without support using a shoe raise for a residual shortening of the right leg of 3.5 cm.

Discussion

In LSNS, skeletal involvement has been reported to include bone cysts, kyphoscoliosis, joint deformities, cranial involvement and vitamin-D-resistant rickets.1,5

The radiological features are absent at birth and biochemical parameters may also be normal. Biochemical abnormalities, muscle weakness, skeletal deformities, delayed motor milestones, rachitic features and fractures develop with growth, and are similar to the progression of tumour-induced rickets/osteomalacia.6

Hypophosphataemic vitamin-D-resistant rickets and osteomalacia have been reported in association with tumours of mesenchymal origin. There are various reports of excision of a bone or soft-tissue tumour leading to improvement of the bone lesions.10 The causal association between hypophosphataemic rickets and LSNS has been suggested by the demonstration of a phosphaturic substance extracted from the skin lesions of a child with LSNS and rickets.10 Several other authors have also proposed a phosphaturic substance theory.11,12

Although the exact chemical nature of the substance is unknown, it has been found to be distinct from parathormone and calcitonin, both known to play a major role in the tubular reabsorption of phosphorus.10 Evidence for a direct phosphaturic effect of the putative tumour-derived factor has also been found.2 Improved renal tubular conservation of phosphate after treatment with vitamin D, oral phosphate, or both, is well documented.6 Shimada et al13 concluded that overproduction of fibroblast growth factor 23 (FGF 23) causes tumour-induced osteomalacia, whereas mutations in the FGF 23 gene result in autosomal dominant hypophosphataemic rickets. The FGF 23 coding is currently being investigated in two of our patients.

In all the reported patients with vitamin-D-resistant rickets associated with epidermal naevus syndrome, including our three patients, rickets was observed at an early age and was associated with marked limb abnormalities, muscle weakness and bone pain.

Treatment of vitamin-D-resistant rickets in association with LSNS with 1,25-dihydroxycholecalciferol and phosphorus supplements has been successful. For example, in the patient described by Oranje et al,7 the radiological findings returned to normal six months after beginning treatment. In our two patients who underwent surgery (cases 1 and 2), radiographs showed normal union of the osteotomies within four months of surgery. Radiologically, rickets can be confused with other skeletal dysplasias, for example metaphyseal dysplasia type Schmid. Biochemical parameters help to confirm one or other diagnosis. One of our patients (case 2) was referred with the diagnosis of “vanishing bone (Gorham’s) disease” due to the severity of the osteopenia.14 In Gorham’s disease, however, the metaphyseal changes of rickets have not been described and the cutaneous angiomas are quite distinct from the linear naevi seen in LSNS.

One of our patients (case 1) showed features resembling fibrous dysplasia in the right tibial shaft (Fig. 1a). Fibrous dysplasia may occur in LSNS alone, or in combination with vitamin-D-resistant rickets. Furthermore, hypophosphataemic rickets has been reported in fibrous dysplasia in the absence of LSNS.15 The skeletal abnormalities of fibrous dysplasia, described in LSNS, include bone cysts, osteopenia, cranial asymmetry, sometimes with involvement of the orbits and facial bones, thoracolumbar scoliosis, unilateral deformity of limbs and chest wall and coxa valga.1,5,16

Although there was no family history of LSNS in any of our patients, familial cases of epidermal naevi have been described with the apparent skipping of generations explained on the basis of autosomal dominant inheritance with decreased penetrance.17 Chromosomal aberrations have been suggested, but not proven as an underlying cause.8

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


