IDIOPATHIC HYPERPHOSPHATASIA WITH DERMAL PIGMENTATION

A TWENTY-YEAR FOLLOW-UP

J. RUDIGER DÖHLER, WILLIAM A. SOUTER, IAN BEGGS, GEORGE D. SMITH

From the Princess Margaret Rose Orthopaedic Hospital, Edinburgh

Hyperphosphatasia, or hereditary bone dysplasia with hyperphosphatasemia, is a rare genetic disorder which is characterised by failure to transform woven into lamellar bone. Clinical, radiological and histological features establish the diagnosis, fractures, deformities, diffuse sclerosis on radiographs and high serum alkaline phosphatase being characteristic.

We report the case of a 27-year-old man with follow-up at the same hospital for 20 years. Attempts at treatment with calcitonin and disodium etidronate (EHDP) failed, but stapling of the growth plates at the knee was successfully performed. Transverse “brittle” fractures of the humerus, lower leg and ribs healed normally, but internal fixation and late bone grafting were required for a subtrochanteric stress fracture of the femur at the age of 24 years. At present the patient has no clinical problems and leads a normal life.

Hyperphosphatasemia due to increased bone turnover is a rare syndrome; although it was recognised three decades ago, only about 20 cases have been reported. A number of names have been given to the disease: these include hereditary, congenital, and chronic idiopathic hyperphosphatasia; juvenile Paget’s disease; chronic familial hyperphosphatasemia; familial osteo-ectasia and osteochalasia desmalis familiaris (Fanconi et al. 1964; Stemmermann 1966; Eyring and Eisenberg 1968; Mitsudo 1971; Iancu et al. 1978). We prefer the descriptive term “hereditary bone dysplasia with hyperphosphatasemia” (Whalen et al. 1977), but have used the shorter, more generally accepted title for this paper.

The purpose of this report is to summarise and discuss the clinical, radiological, biochemical and pathological findings in a patient with this disease who has been under care at the same hospital for 20 years.

CASE REPORT

Family history. The patient’s maternal grandmother was thought to have had rickets in childhood and walked...
using calipers until she was eight years old. The remainder of the family, including a younger brother and a younger sister of the patient, are reported to be healthy.

**Paediatric history.** At birth, in 1957, the patient had brown pigmented areas on the face, neck and back; these have persisted (Figs 1 and 11). Chromosome studies in 1968 and 1973 showed a normal male karyotype. While a child he was said to get breathless on exertion, and at the age of 16 years, he looked physically immature and his sexual development was retarded by about two years. His teeth were normal and remain so.

In 1973, a diagnosis of idiopathic hyperphosphatasia was established, serum levels of alkaline phosphatase being persistently high. A mitral systolic murmur was heard and an ECG suggested slight left ventricular hypertrophy. Slight temporary neural loss of hearing was noted and may have been related to the bony involvement of the base of his skull. Three fits were observed in this year. EEG studies showed discharges on flicker stimulation, but anticonvulsants were not given and there were no more convulsions after 1976.

**Metabolic assessment.** In 1973 the patient was admitted to the Metabolic Unit of the Western General Hospital in Edinburgh for detailed metabolic assessment. The findings were inconclusive and there was no useful response to calcitonin (see Fig. 12), but his cyclic AMP excretion suggested that calcitonin had stimulated his parathyroids. A later study of the effect of disodium etidronate (EHDP), 700 mg per day, showed no evidence of any therapeutic value. However, a marked increase in calcium excretion was induced by the daily administration of a combination of EHDP 700 mg orally and salmon calcitonin 500 mg intramuscularly. Calcium excretion returned to normal on withdrawal of the calcitonin. Hydroxyproline excretion remained normal during the administration of these drugs.

**Orthopaedic history.** At the age of seven years, in 1964, the patient presented with bilateral genu valgum, intermalleolar separation being 9 cm (Fig. 1). No treatment was advised. One year later, a partial stress fracture of the right femoral neck was treated in long leg plaster cylinders. By 1968, the knock-knee had deteriorated to
Figures 6 and 7  Radiographs at the age of 23 years. The pelvis shows generalised bony sclerosis with areas of rarefaction, and there is bilateral coxa vara. The skull is diffusely sclerotic and expanded, with particular involvement of the base. There are multiple lucent areas but the diploe, mastoid air spaces and sinuses are obliterated.

Fig. 8  Transverse subtrochanteric fracture of the femur sustained at the age of 24 years.

15 cm of malleolar separation, and bilateral osteotomies of proximal tibia and distal femur were undertaken through remarkably solid bone which healed without complications, as did a transverse fracture of the left humeral shaft in 1969 (Fig. 2).

By 1973, bilateral genu valgum had recurred with slight flexion deformity on the right and a recurvatum deformity on the left. The gap between the malleoli was 16 cm. Apart from considerable hypermobility of some joints no other orthopaedic abnormalities were seen. The intermalleolar gap increased and bilateral stapling of the medial femoral and tibial epiphyses was performed.

In 1974, there was a possible rib fracture (Fig. 3) and a fracture of the left leg needed closed reduction. Radiographs of the hands showed diffuse changes (Fig. 4). Intermalleolar separation had improved to 4 cm, but by 1976 varus deformity of the knees was evident (Fig. 5) and the medial staples were removed and lateral staples inserted in both knees. In 1980, radiographs of the pelvis and the skull (Figs 6 and 7) showed gross changes.

In 1981, the patient suffered a subtrochanteric stress fracture of the left femur (Fig. 8) which required internal

Fig. 9

Bone biopsies from the femur at the age of 17 years. Figure 9  There is a lattice of broad trabeculae of woven bone with intervening fibrous stroma (haematoxylin and eosin, × 35). Figure 10—Irregular cement lines are prominent and there is focal osteoclastic activity. The surfaces of the trabeculae show fine irregularities which blend into the delicate fibrous stroma (haematoxylin and eosin, × 115).
fixation; this was complicated by staphylococcal septicaemia from an infected haematoma which healed with drainage and systemic antibiotics. However, non-union of the fracture later required bone grafting. All his fractures showed a clean, “brittle” break like that in a stick of chalk (Figs 2 and 8).

**Pathology.** Bone biopsies were obtained from the left iliac crest in 1965 and subsequently from operation sites in the femur and tibia, and from the right iliac crest in 1968, 1973, 1976 and 1982. All specimens showed similar features, both cortical and cancellous bone being transformed into a lattice of broad, coarse-fibre woven-bone trabeculae (Fig. 9) with prominent cement lines arranged in an irregular, but not quite pagetoid fashion (Fig. 10). The surface of the trabeculae displayed a fine irregularity; osteoclastic activity was sparse and few “epitheloid” osteoblasts were seen. The intervening fibrous stroma, largely replacing haemopoietic marrow, included bland fibroblastic cells regularly distributed amongst delicate connective tissue fibres (Fig. 10); the bony trabeculae appeared to be derived directly from this stroma by metaplasia. This picture resembled that of fibrous dysplasia of bone, except for the presence of a continuous bony trabecular meshwork. Hypermobile joints and marked lumbar hyperlordosis persist but the main problem is varus deformity of the left hip and knee joints, resulting in 2 cm of shortening (Fig. 11). However, the patient is able to lead a normal life and requires no treatment.

**DISCUSSION**

Idiopathic hyperphosphatasia, or hereditary bone dysplasia with hyperphosphatasemia, is inherited as an autosomal recessive (Mitsudo 1971). It is a disorder of growing membranous bone in which primitive fibrous bone fails to mature into compact Haversian bone, with concurrently increased turnover of bone and collagen (Caffey 1973, cited by Iancu et al. 1978). The findings in our patient fit well with those of previous reports, but despite this the diagnosis for 10 years was felt to be “Albright’s disease”. This assumption could be supported by the similarity of the radiographic and histological findings and the raised alkaline phosphatase (Döhler and Hughes 1986), but an elevated alkaline phosphatase level is not mandatory for a diagnosis of polyostotic fibrous dysplasia and may not be the only biochemical abnormality or even be present at all times or in all patients suffering from hyperphosphatasia (Stemmermann 1966). Our patient had consistently very high serum levels of alkaline phosphatase; acid phosphatase and lactate dehydrogenase levels were also raised, but the serum thyroxine was low on the one occasion it was measured (Table 1).

Cafe-au-lait pigmentation is frequently seen in patients with polyostotic fibrous dysplasia of bone, this representing incomplete or, with precocious puberty, classic Albright’s syndrome. Our patient is apparently the first reported with skin pigmentation in hyperphosphatasia. The diagnosis is established by a mosaic of pathological, radiographic, and clinical findings.

**Pathological concept.** Idiopathic hyperphosphatasia is a disorder of the modelling of bone and the basic pathology is thought to be a block to the transformation of coarsely woven bone into mature lamellar bone. This results in an inherently weak skeleton with attenuation of diaphyseal cortices. Tetracycline labelling has shown an increased mass of osteogenic tissue, while histochemical studies show that not only is the alkaline phosphatase level raised, but also those of acid phosphatase, amino-peptidase, lactate dehydrogenase, acid glycocomglycans and reticulin (Stemmermann 1966). By contrast, fibrous dysplasia of bone shows insufficient osteogenesis within the fibrous tissue to form a continuous trabecular framework. In Paget’s disease, there is excess surface osteoclastia, but this is unlikely to be important in hyperphosphatasia because few osteoclasts are seen. Excessive osteocytic osteolysis has, however, been reported by Whalen et al. (1977).

**Radiology.** The increased amount of osteogenic tissue is represented by diffuse sclerosis although areas of rarefaction are also present. There is an undertubulation of the long bones as seen in Figures 2, 4 and 5. A major difference between hyperphosphatasia and Camurati–Engelmann disease is that the latter is predominantly

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**Fig. 11**

The patient at the age of 27 years, showing skin pigmentation and varus deformity of the left leg.
Table I. Biochemical results, with mean plasma levels of ions and enzymes during follow-up

<table>
<thead>
<tr>
<th>Year</th>
<th>Calcium</th>
<th>Phosphate</th>
<th>Alkaline phosphatase</th>
<th>Acid phosphatase</th>
<th>Lactic dehydrogenase</th>
<th>Thyroxine</th>
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<tr>
<td>1965</td>
<td>2.2</td>
<td>1.6</td>
<td>561.6</td>
<td>22.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1968</td>
<td>2.8</td>
<td>1.38</td>
<td>752.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1973</td>
<td>2.37</td>
<td>1.5</td>
<td>470.4</td>
<td>47.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1976</td>
<td>2.3</td>
<td>1.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1981</td>
<td>2.6</td>
<td>1.1</td>
<td>461.8</td>
<td>—</td>
<td>352</td>
<td>45</td>
</tr>
<tr>
<td>1982</td>
<td>2.3</td>
<td>0.82</td>
<td>930.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Calcium and inorganic phosphorus in mmol/l.
Alkaline phosphatase, formol-stable acid phosphatase and urea-stable lactate dehydrogenase in units/l.
Thyroxine in mmol/l.

diaphyseal, sparing the bone ends. Diffuse skeletal involvement distinguishes hyperphosphatasia from Paget’s disease and this is confirmed by widespread increase in uptake of radionuclide on bone scintigraphy. This investigation is also useful in monitoring the disease and the results of biochemical treatment (Iancu et al. 1978).

Clinical aspects. Lack of mature lamellar bone gives a risk of pathological fracture. The increased osteogenic tissue may lead to early healing (Fanconi et al. 1964), but this was not seen in our patient. Unlike the situation in polyostotic fibrous dysplasia, deformity in hyperphosphatasia rarely requires major surgery, though Eyring and Eisenberg (1968) reported the use of bilateral closing-wedge osteotomies of the tibiae in two siblings, and in our patient stapling of the growth plates at the knee was used. Gross deformity of the axial skeleton has also been reported (Iancu et al. 1978). Early deformity is felt to be a poor prognostic sign.

Our patient gained no benefit from calcitonin and disodium etidronate (Fig. 12), though Whalen et al. (1977) reported radiological and histological response to calcitonin in two children suffering from hyperphosphatasia, and Woodhouse et al. (1972) reported a response to human calcitonin in a five-year-old boy suffering from juvenile Paget’s disease. Hjelmstedt and Ljunghall (1979) obtained no response in a 23-year-old woman with classic Albright’s syndrome.

Subclinical hearing loss and profound deafness have been noted in some previous cases (Eyring and Eisenberg 1968; Iancu et al. 1978), while blurred vision was present in two patients (Mitsudo 1971; Iancu et al. 1978). These complications could result from atrophy of the auditory and optic nerves following encroachment of the hyperplastic bone on the foramina (Mitsudo 1971). Our patient had massive involvement of the base of the skull

Diagram to show the levels of hydroxyproline and alkaline phosphatase during a period of treatment with calcitonin. There was no useful response. (Figure by courtesy of Professor Emeritus J. A. Strong, Edinburgh.)
and the facial bones (Fig. 7), but his hearing loss was transient. Epilepsy has not previously been reported. Cardiomegaly and hypertension have been reported in a few patients (Iancu et al. 1978), but the minor cardiac signs in our patient, at the age of 16 years, have settled, leaving no signs of cardiovascular insufficiency or hypertension at this time.

Coincidental benign soft tissue tumours have been reported in Albright's syndrome (Logel 1976) and in hyperphosphatasia, and may possibly be related to abnormal structure and metabolism of connective tissue collagen and elastin (Mitsudo 1971). Our patient had no tumours but the dermal pigmentation could be related to the underlying genetic defect in mesenchymal tissue.

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REFERENCES


