POLYOSTOTIC FIBROUS DYSPLASIA—ALBRIGHT’S SYNDROME

A Review of the Literature and Report of Four Male Cases, Two of which were associated with Precocious Puberty

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Polyostotic fibrous dysplasia is a rare disease of the skeleton. Despite much speculation the etiology remains obscure. At this stage of our understanding of the disease, which is of interest to physicians, pediatricians, radiologists and orthopaedic surgeons, it is desirable that a detailed record of new examples should be made as they arise.

NOMENCLATURE

Lichtenstein (1938) introduced the term polyostotic fibrous dysplasia to designate “a skeletal developmental abnormality affecting one, several, or many bones with a predominantly unilateral distribution.” Reports of similar cases had occurred before, but under a bewildering variety of titles.

Some cases, with widespread skeletal lesions, also show other changes. Albright, Butler, Hampton, and Smith (1937) described the association of predominantly unilateral skeletal changes with pigmentation of the skin, and with precocious puberty in females. This syndrome now bears Albright’s name. The first recorded case appears to be that of Weil (1922). Recently Dockerty, Ghormley, Kennedy and Pugh (1945) analysed thirty-three cases from the literature and added six of their own.

CLINICAL FEATURES

The condition is a disorder of childhood which becomes arrested in adult life. The sexes are affected equally. The expectation of life is not diminished, but deformities and pathological fractures are common. In addition to the features which characterise Albright’s syndrome, polyostotic fibrous dysplasia may be associated with other endocrine changes. Enlargement of the thyroid gland was found in five of twenty-five cases extracted from the literature of the previous decade by Falconer and Cope (1942); two of these had thyrotoxicosis. These authors also reported two cases of widespread bone disease with non-toxic enlargement of the thyroid gland and some manifestations of acromegaly. Peck and Sage (1944) reported a case in which there was toxic goitre with acromegaly, and diabetes mellitus from which the patient died.

In addition to endocrine changes, certain congenital abnormalities have been observed, but their association may be fortuitous. Stauffer (1941) described a case with arteriovenous aneurisms. Osgood (1946) reported a patient in whom the dysplasia co-existed with osteopoikilosis but other manifestations of Albright’s syndrome were not present. Two cases are on record in which the osseous dysplasia was accompanied by multiple soft tissue tumours. Uehlinger (1940) recorded the case of a man who died at the age of sixty-seven and had suffered, since childhood, from widespread fibrous dysplasia of the skeleton with multiple soft tissue tumours of similar histological appearances to those of the affected bones.

Sexual precocity in the male has seldom been observed; indeed as recently as 1947, Bogart and Imler stated that precocious puberty was limited to female cases. Lange (1938), and Falconer and Cope (1942), reported precocious puberty in two boys aged eight and ten years respectively. Two of the four cases reported in this article, all of which were males,
developed secondary sex characters during the first decade. In contrast to sexual precocity is the case of Moehlig and Schreiber (1940) where a boy of sixteen with multiple bone lesions had no beard, or axillary hair; he had pubic hair of female distribution, and a puerile voice.

RADIOGRAPHIC APPEARANCES

Radiographic features of the dysplasia consist of multiple localised lesions with normal bone elsewhere. According to the distribution of the affected bones the disease may be monostotic, monomelic, unilateral, or bilateral. The vertebral column is seldom affected. Areas of rarefaction and expansion are often found which, in the radiographs, resemble true cysts. The affected bones show a "ground glass" appearance in which homogeneous areas of increased or decreased density are present with thinning of the overlying cortex. The epiphyses are seldom affected, and then only after union with the shaft. Fusion may, however, occur prematurely. The base of the skull often shows enormous hypertrophy of dense bone which may obliterate the nasal sinuses and compress the cranial nerves. Great thickening of the calvarium, often resembling the changes of Paget's disease and especially when involving the base of the skull, may present a striking feature which is of diagnostic importance. In some bones there is only slight coarsening of trabeculation, but it is reasonable to suppose that in these questionable areas the pathological process is not yet so advanced as to have established radiological evidence. Albright et al. (1937) drew attention to similarity between the radiographic appearances of fibrous dysplasia and healing parathyroid osteodystrophy after parathyroidectomy.

PATHOLOGY

The skeletal changes have been described by Albright et al. (1937), Uehlinger (1940), Lichtenstein and Jaffe (1942), and Falconer and Cope (1942). Uehlinger stated that the marrow spaces are the site of proliferation of relatively avascular and acellular fibrous tissue which leads to expansion and thinning of the cortex. The long bones and the neighbouring bones of the limb girdles are most often affected and the "shepherd's crook" of the femur—a coxa vara deformity—is characteristic. The disease affects primarily the diaphysis: it is exceptional for the epiphyses to be affected. True cysts, giant-cell tumours, inflammatory changes, and neoplastic changes, do not occur. The base of the skull and the bones of the vault are often the site of gross changes which have recently been described by Windholz (1947).
in a paper in which the relationship between fibrous dysplasia and leontiasis ossia is discussed. Blood chemistry—No constant changes are found in the blood chemistry other than elevation of the alkaline phosphatase if the bone changes are widespread.

ETIOLOGY

The etiology of the skeletal and extraskeletal changes is not understood. The most recent comprehensive surveys of current ideas are to be found in the monographs of Forst and Shapiro (1943), Falconer and Cope (1942), and Dockerty et al. (1945). Falconer and Cope suggested that the association with polyostotic fibrous dysplasia of endocrine disturbance and cutaneous pigmentation was one of independent variables; and that the distinction between the dysplasia on the one hand, and Albright's syndrome on the other, was one of degree. They believe that a common etiological basis must exist because the features of Albright's syndrome occur with such frequency in cases showing disseminated bone lesions. It is generally accepted that the disease must be due to a disturbance of undifferentiated mesenchyme in early embryonic life. Heredity appears to play no part. The only convincing example of a familial incidence was that of Hirsch (1929) where three siblings were affected. Several cases have been described in which icterus gravis neonatorum had occurred (Braid 1939), but these constitute a very small proportion of the recorded cases and it seems unlikely that the association is of significance.

DIFFERENTIAL DIAGNOSIS

Polyostotic fibrous dysplasia may be confused with hyperparathyroidism, Paget's disease, Ollier's disease, osteogenesis imperfecta tarda, and the lipoid reticuloses. In monostotic cases a number of other conditions will have to be considered, amongst which are neurofibromatosis and osteoclastoma. Hyperparathyroidism is characterised by general skeletal decalcification and typical changes in the blood calcium and phosphorus levels, high alkaline phosphatase, and increased excretion of calcium.

Paget's disease is rare under the age of forty years and is usually associated with thickening of cortical bone. The only close resemblance with fibrous dysplasia is in the changes which occur in the calvarium.

Ollier's disease (skeletal enchondromatosis) shows sharply defined lesions in the cartilage bones which are usually short with broad and irregular metaphyses.

Xanthomatosis and Gaucher's disease are likely to present other stigmata such as the manifestations of Hans-Schüller-Christian's syndrome in the first disease, and splenomegaly in the other, with characteristic appearances in the marrow film obtained by sternal puncture. Osteogenesis imperfecta tarda may resemble fibrous dysplasia in the history of repeated fractures and in the ground-glass appearance of the bones in radiographs. It differs in that there may be a family history of the condition; the bones are usually slender and often decalcified; the manifestations in the skull are different; and the vertebral bodies are flattened.

TREATMENT AND PROGNOSIS

Polyostotic fibrous dysplasia does not reduce the expectation of life. Fresh lesions cease to appear when maturity is reached. No medicinal therapy has been found to have any effect upon the disease, and treatment is necessarily limited to the management of fractures and deformities.

CASE REPORTS

Case 1. J. M., barber, aged twenty-five years (Figs. 1–8), had walked with a limp since the age of eight. He sustained a pathological fracture of the left femur when aged eleven. At intervals, since then, he has suffered fractures of the right femur, left radius, left ulna and left humerus. At the age of thirteen his voice broke and secondary sex characteristics appeared. There was no history of icterus neonatorum and no relevant family history.
Case 1. There is deformity of the right upper and lower jaws, and palpable bosses above the hairline (Fig. 2). The right mandible is expanded and shows mottled areas of rarefaction and sclerosis.

Case 1. There is much thickening of the parietal bones and hyperostosis of the base of the skull.
On examination he exhibits marked facial asymmetry and deformity of the left mandible (Fig. 2). There is a patch of brown pigmentation in the lumbar region. The left leg is shorter than the right. There are visible and palpable irregularities of the ribs. He has a large "cyst" in the right humerus which is fractured in two places (Fig. 7), but, despite this, he is able to continue his work with no support for the limb.

Case 1. The right humerus at the age of eleven years (Fig. 5). At the age of fourteen years a fracture of the upper shaft of the bone was sustained (Fig. 6). At the present time the patient is aged twenty-five years, and despite the fact that two fractures have now been sustained, and that the bone shows very extensive "cystic" changes and expansion of the shaft, no external support is needed and the patient continues his work as a barber (Fig. 7).

Blood chemistry (November 1947):

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>9.0 mgm. per 100 c.c.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.2 mgm. per 100 c.c.</td>
</tr>
<tr>
<td>Urea</td>
<td>43 mgm. per 100 c.c.</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>17.4 units (Jenner and Kay)</td>
</tr>
<tr>
<td>Urea concentration test</td>
<td>3.55 per cent</td>
</tr>
<tr>
<td>Urea clearance test</td>
<td>80 per cent. of normal</td>
</tr>
</tbody>
</table>

Radiographic appearances—The distribution of skeletal lesions is shown in the diagram (Fig. 1). The skull shows gross changes in the calvarium which simulate Paget's disease (Fig. 4), and marked hypertrophy
of the base, the mastoid processes and the sphenoid bone. The bones show a typical "ground glass" appearance but there are many "cystic" areas in the ribs, the right humerus, and the right femur. The "shepherd's crook" deformity of the right femur developed between 1934 and 1936 (Fig. 8). Gross changes in the right humerus have occurred in the last ten years (Figs. 5-7).

Comment—This case exhibits bone changes typical of polyostotic fibrous dysplasia, and there is a patch of cutaneous pigmentation, but the third stigma of Albright's syndrome—sexual precocity—is lacking.

Case 2. J. M., schoolboy, aged eleven years, has since the age of three years sustained three fractures of the left tibia and fibula, a fracture of both femora, and a fracture of the left radius and ulna. Two years ago a "cyst" of the left femur was curetted and bone chips were inserted. Since birth he has had a patch of brown pigmentation over the posterior aspect of the right shoulder and arm. At the age of eight years his voice broke and pubic hair appeared. There is no history of icterus neonatorum and no relevant family history. On examination he appears older than his years. His height is 5 feet 11 inches; and weight just over 7 stones (99 pounds). There is prominence of the left frontal and parietal regions. The thyroid gland is not enlarged. The genitalia appear to be mature. His physical appearance is shown in Fig. 9.

Blood chemistry: Calcium, 10.9 mgm. per 100 c.c. Phosphorus, 3.3 mgm. per 100 c.c. Alkaline phosphatase, 510 units (Jenner and Kay). Urea, 35.0 mgm. per 100 c.c.

Radiographic appearances—The distribution of skeletal lesions is shown in the diagram (Fig. 1). The affected bones are irregularly expanded and show a "ground glass" appearance as well as "cystic" areas.
The epiphyses of his elbows suggest some precocity since fusion of the capitellum and trochlea with the humeral shaft is almost complete. The skull exhibits great thickening of the left parietal and both mastoid regions; the left halves of the middle and anterior cranial fossae show similar gross changes and the sphenoid sinus is obliterated (Fig. 10). The left ethmoid and maxilla are also involved. The left femoral neck and upper part of the shaft are "cystic" but although there is a symptomless pathological fracture there is not yet coxa vara deformity. In this case, the insertion of bone chips does not seem to have led to ossification of the abnormal area.

Comment—This case presents a typical radiological picture of polyostotic fibrous dysplasia and the bone changes are also associated with cutaneous pigmentation and precocious puberty.
Case 3. A. T., schoolboy, aged thirteen years, was admitted with a fracture of the shaft of the left femur sustained while boxing. There was no history of previous fractures but since the age of seven, cramp-like pain has been felt occasionally in the left thigh. There is no history of icterus neonatorum and no relevant family history. On examination he is a small healthy looking boy, height 4 feet 10 inches, weight 54 stone (77 pounds). There is extensive pigmentation of the right leg, thigh, and buttock. Secondary sex characteristics have not yet appeared.

Blood chemistry:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>10.7 mgm. per 100 c.c.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3.2 mgm. per 100 c.c.</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>25.7 units (Jenner and Kay)</td>
</tr>
<tr>
<td>Urea clearance test</td>
<td>43 per cent. repeat = 59 per cent. of normal</td>
</tr>
<tr>
<td>Urea concentration test</td>
<td>2.76 per cent. repeat = 2.9 per cent. of normal</td>
</tr>
<tr>
<td>Calcium balance test</td>
<td>Normal</td>
</tr>
</tbody>
</table>

The tests suggested some impairment of renal function but there was no albuminuria, and intravenous pyelography showed no abnormality.

Radiographic appearances—The distribution of the lesions is shown in the diagram (Fig. 1). They consist almost entirely of areas of expansion where the cortex is thin, and the normal architecture is replaced by the structureless “ground glass” appearance. The skull is unaffected. There is mild coxa vara deformity of the left femoral neck where little normal bone is visible; but on the right side there is a bridge of normal bone in this position and no coxa vara. Most of the affected bones show uniform increase in breadth.

Comment—This case shows widespread skeletal involvement, bilateral in distribution, with cutaneous pigmentation but no other apparent abnormalities.

Case 4. T. W., male, aged sixteen years—At the age of three months pigmentation of the buttocks and right thigh was noticed and at five years of age facial deformity became evident. In 1942, when he was ten, he was examined by Dr Court who observed that the skull and face were large and deformed, the hands and feet large, and the size of the right upper limb greater than that of the left. There was sexual and skeletal precocity. His genitalia were pubescent and he was tall for his age.

Blood chemistry (1942)—

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tbody>
<tr>
<td>Serum calcium</td>
<td>10.4 mgm. per cent.</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>3.3 mgm. per cent.</td>
</tr>
<tr>
<td>Blood urea</td>
<td>21 mgm. per cent.</td>
</tr>
<tr>
<td>Urea clearance test</td>
<td>145 per cent. normal.</td>
</tr>
<tr>
<td>Plasma cholesterol</td>
<td>119 mgm. per cent.</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>43 units</td>
</tr>
<tr>
<td>Urine</td>
<td>Normal</td>
</tr>
<tr>
<td>Glucose tolerance test</td>
<td>Normal</td>
</tr>
<tr>
<td>Blood W.R. and Kahn tests</td>
<td>Normal</td>
</tr>
<tr>
<td>Rh positive (in 1944)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Ophthalmological examination—Normal.

Radiographic appearances (1948)—The left fourth and seventh ribs are abnormal in shape and structure, showing no differentiation between the cortex and medulla, and no trabeculation. The base of the skull shows marked hyperostosis. The squamous part of the occipital bone is expanded, and the maxillae are so grossly affected that the antra are almost completely obliterated. The mandible is expanded, especially on the left side, and normal trabeculation is replaced by the homogeneous “ground glass” appearance of fibrous dysplasia. No convincing changes are seen in the rest of the skeleton.

Comment—This case shows characteristic bone changes affecting the skull and two ribs. No “cysts” are present in any bones. The skeletal precocity is perhaps evidence of endocrine disturbance, and the presence of a large area of pigmentation affords additional evidence by which to support the diagnosis of Albright’s syndrome. (This patient has been under the care of Dr Court for four years and has been investigated by Dr Donald Hunter who established the diagnosis of Albright’s syndrome.)
POLYOSTOTIC FIBROUS DYSPLASIA—ALBRIGHT'S SYNDROME

SUMMARY

1. Four cases of polyostotic fibrous dysplasia are presented.
2. All are males, all show cutaneous pigmentation, and in two there has been precocious puberty.
3. The literature has been reviewed, and present conceptions of the pathology and etiology of the disease have been discussed.
4. The dysplasia if often confused with parathyroid osteodystrophy and sometimes the parathyroid glands are needlessly explored. This confusion should not arise if it is remembered that no general skeletal decalcification, and no constant changes in the blood calcium or phosphorus, occur in polyostotic fibrous dysplasia. The radiographic appearances of healing parathyroid osteodystrophy are, however, indistinguishable.
5. No effective therapy has been discovered for this disease. Pathological fractures and deformities may require treatment.

I must express my thanks to Professor Nattrass, Mr Gordon Irwin, and Mr Jones, of the Royal Victoria Infirmary, Newcastle upon Tyne; and to Mr Reid of Middlesbrough, for permission to publish these cases. I have also to thank Dr Donald Court for much helpful criticism, the staff of the Hospital for Sick Children for the opportunity to study radiographs of Case 4, and Mr E. Forster for his help in the preparation of illustrations.

REFERENCES