CLINICAL REVIEW

Bone sclerosis in infancy

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Summary

The significance of bone sclerosis in infants and children as seen on X-ray examination is discussed.

The recognition of increased bone density during the investigation of infants who fail to thrive may not establish the diagnosis but is important in instigating further tests.

This review draws attention to the practical value of recognizing a generalized increase of bone density, especially as an incidental finding. Since the immediate reaction of growing bone to metabolic insult is limited, there is considerable overlap in the radiographic features of different conditions, but clinical and biochemical measures can then be directed towards a correct assessment.

Introduction

The opacification of bone depends upon the distribution of calcium salts in an intercellular ground substance which is apparently evolved by special cells of the connective tissue series—first chondroid from chondroblasts then osteoid from osteoblasts. In the adult the fibres of this matrix are arranged in sheets or lamellae. In infants they form a non-lamellar felt-work.

Resorption of bone is probably effected by the osteoclast. The balance between the activity of osteoblast and osteoclast determines the growth and shaping of bone and the formation of its internal structure. Osteoclasts can act only on calcified matrix and according to Snapper (1957a) do not function before the infant is 8 months old. Several workers, including Johnston & Deiss (1966) have shown that calcitonin causes bone sclerosis by interfering with bone resorption. Foster *et al.* (1966) demonstrated increased trabecular bone at the metaphyses of parathyroidectomized rats treated with calcitonin, with increase in spongiosa and a significant reduction in osteoclasts at these sites. From the literature (Snapper, 1957b; Shapiro, 1962; Stan-

bury, 1962; Aegerter & Kirkpatrick, 1963), it seems that interference with osteoclastic activity either from failure of cellular function or because of unsuitable substrate, leads to excessive skeletal retention of calcium. Infant bone is peculiarly sensitive owing to the rapid turnover of its constituents. Some of the causes are illustrated by these case reports.

Material and methods

The illustrative cases considered presented in the routine work of a general children's hospital in a 5-year period. In the absence of opportunity for step-wedge densitometry in this retrospective study bone density was assessed relative to soft tissue opacity as compared with 'normal' casualty cases X-rayed with the same factors (48 kV, 4.4 mAS 100 cm. Standard screens and films). Increase in density when not accompanied by disturbance of osseous outline was interpreted as osteosclerosis (Collins, 1966).

Sclerosing renal osteodystrophy

The mechanism of the sclerotic process is not known. Renal failure interferes with absorption of calcium from the gut (Grainger, 1964) and allows calcium loss as base in the urine. Ginzler & Jaffe (1941) and Lalli & Lapidus (1965) suggest that renal acidosis leads to malacia but as the renal disease improves, excessive recalcification may cause sclerosis. Bone biopsy in five of seven chronic cases reported by Wolf & Denko (1958) showed dense cortical bone with little cellular activity. Sussman & Poppel (1942) mention osteosclerosis in protracted cases and Davis (1953) reported combined productive and destructive bone lesions at autopsy. Karani (1955) suggested that secondary hyperparathyroidism due to low blood calcium stimulates both osteoclasts and osteoblasts. Cysts and sub-periosteal erosions indicative of hyperparathyroidism were found by Craven (1964) in all but two of fifteen adults with sclerosing renal osteodystrophy but

no sclerosis occurred in the two infants in his series. Sclerosis is said to occur only when hyperparathyroidism is associated with uraemia, (Beveridge, Vaughan & Walters, 1959), never with hyperparathyroidism alone (Fraser, 1964).

Case 1

E.P. Born 4 November 1958. From a few days of age he suffered from recurrent urinary infections. Investigations showed gross bilateral pyelonephritis with ureteric reflux and dilation, without identifiable obstruction in the urethra or bladder neck. The lumbar spine appeared normal in pyelograms done before July 1959. He remained in fair general health, although stunted, until 1962 when his blood urea was 69 mg/100 ml, and serum calcium 10 mg/100 ml. Hand and wrist films showed unusually dense epiphyseal plates without sub-periosteal erosions or rachitic changes. Micturating cystogram, a year later, showed a dense coarse trabeculation in the lumbar spine, pelvis and ribs, and a similar pattern, which resembled recalcified malacic bone, in wrist and knee (Fig. 1a, b and c). The phalanges are not included so that the presence

or absence of hyperparathyroid erosions could not be established. Owing to the gap in attendance a phase of under calcification may have been missed. Sclerosis was well established at 3 years of age.

Case 2

J.McL. Born 8 May 1962. Admitted March 1963 with pyrexia and a history of constipation and failure to thrive. Investigation disclosed a basal systolic murmur, renal infection and a blood urea of 100 mg/100 ml. Intravenous pyelogram showed pyelonephritic changes in the kidneys accompanied by increased density of the spine, femora, skull and wrist (Fig. 2). Serum calcium was 12.6 mg/100 ml and remained elevated with a low calcium diet. Six months later the urinary infection was controlled but the serum calcium was 14.4 mg/100 ml, blood urea 69 mg/100 ml. He was re-admitted in June 1964 with a recurrence of urinary infection and died without further radiological studies. The serum calcium was then 9.3 mg/100 ml and blood urea 30 mg/100 ml. At necropsy 'small yellow stones' were found in pyelonephritic kidneys. There was

FIG. 1. E.P. Pyelonephritis. (a) Micturating cystogram with coarse dense bony pattern in spine and pelvis. (b) and (c) Similar appearance in wrist and knee.

FIG. 2. J.McL. Pyelonephritis. Increased density of spine, pelvis and metaphyses.

no macroscopic lesion in the parathyroids, heart or great vessels.

The basal systolic murmur suggested idiopathic hypercalcaemia but the failure of the serum calcium to fall with a reduced calcium intake and the degree of renal damage were more in keeping with renal osteodystrophy. The low terminal serum calcium may have resulted from the increased elimination of calcium and the deposition of stones.

Idiopathic hypercalcaemia

Hypercalcaemia in infancy associated with mental defect, osteosclerosis, a typical facies, varying degrees of renal impairment and a systolic heart murmur has been reported by Butler (1951), Fanconi (1951), Lightwood (1952a, b), Payne (1952) and Fanconi *et al.* (1952). Mild cases present as failure to thrive, more severe cases terminate in renal failure. More recently supra-aortic stenosis has been described in this syndrome (Black & Bonham Carter, 1963; Garcia *et al.*, 1964; Black, Butler & Schlesinger, 1965).

FIG. 3. C.K. Hypercalcaemia. Increased density of wrist and metaphyses.

In the period 1953–55 there were approximately 100 cases each year in Britain as compared with twelve cases in U.S.A. (Fraser, 1961), and ten cases in Australia in the 5 years 1954–59 (Clements, McDonald & Williams, 1961). The reason was said by Creery & Neill (1955) to be the excess of vitamin D added to footstuffs in Britain. Unusual sensitivity of some children to vitamin D may be a factor (Lowe *et al.*, 1954). Lindquist (1962) mentions features which do not tally with hypervitaminosis D, including the total absence of porosis. Eban (1961) reviewing the pathology and radiology of this condition reported areas of porosis in some of his cases. He suggested that the pathological process is that of cell poisoning. An extensive lattice of calcified cartilage is formed in which the toxic

FIG. 4. B.H. Hypercalcaemia. (a) Increased density of wrist and metaphyses. (b) Increased density of skull.

heavy metal is embedded, whether it is lead, bismuth, strontium or calcium. Osteoblasts are reduced and there is little new bone formation, but if the metabolic state becomes normal this layer is absorbed in about 2 years. Typically the skull, spine and metaphyses are denser than normal on X-ray.

Case 3

C.L. Born 19 June 1965. Admitted aged 12 months weighing 14 lb 7 oz with a history of vomiting from the age of 3 months. Retarded ossification with increased bone density (Fig. 3) was associated with a serum calcium of 11.8 mg/100 ml and a blood urea of 57 mg/100 ml. Urinary investigations including excretory urograms were normal. Rapid clinical improvement followed a low calcium diet, and in 6 weeks the blood calcium was 9.4 mg/100 ml and the blood urea 42 mg/100 ml and subsequent progress was satisfactory.

Case 4

Admitted aged 15 months with 6 months' history of vomiting, constipation, failure to thrive

and inability to sit up. Muscle tone was poor. X-ray of wrist, spine and knees showed sclerosis at the epiphyses and the vertebral bodies (Fig. 4a). In the skull views the calvarium was dense and thick (Fig. 4b). Serum calcium 16 mg/100 ml. The blood urea was transiently elevated to 95 mg/100 ml, probably as a result of vomiting and dehydration.

A low-calcium, low-vitamin-D diet reduced the serum calcium to 10 mg/100 ml with restoration of normal physical health. Some mental retardation persisted. It was discovered that the child had lived from birth solely upon milk, supplemented by an unknown quantity of vitamin D. The consequent clinical and radiological findings were indistinguishable from those of the 'idiopathic' syndrome.

Lead poisoning

The toxic action of lead on bone resembles that of excess calcium in producing a fibrous meshwork at the metaphysis which becomes overcalcified. In mild cases it may be impossible to say whether dense bands at the metaphyses are due to lead poisoning or to arrested bone growth from other causes (Caffey, 1967). The

sclerotic metaphyses shown in Fig. 5 (K.O'B.) were accompanied by a blood level of $275 \mu\text{g}/100 \text{ ml}$ in an infant with failure to thrive.

FIG. 5. K.O'B. Lead poisoning, Increased density of metaphyses.

Cretinism

In 1906 Dieterle remarked on the hardness of myxoedematous bone. A ring of sclerosis around epiphyseal centres is common in cretinism but general sclerosis is less frequent. Braid (1951) in a survey of thirty cases mentions only increased density of the zone of provisional calcification. Increase in density associated with nephrocalcinosis in cretinism is reported by Naylor (1955) and by Tumay, Bilger & Hatemi (1962). Some cases showed a rise of serum calcium before treatment and some during treatment. They suggested a disorder in sterol breakdown and referred to the hypersensitivity to

vitamin D of thyroidectomized animals (Krane *et al.*, 1956). A decrease in calcium turnover in bones due to insufficient osteoclastic activity is an alternative explanation, Jeune & Muller (1959) found two cases with osteosclerosis, both with a normal serum calcium, among ninety three cases of hypothyroidism. In a 2-year-old child, meta-static calcification in the thigh muscles accompanied increased density of the skull trunk-bones and ends of the long bones. The blood urea was $72 \text{ mg}/100 \text{ ml}$. After 18 months' thyroid therapy the soft tissue calcification disappeared and the bones became slightly under-mineralized. Renal calcification was noted but the blood urea dropped to $31 \text{ mg}/100 \text{ ml}$. The bones of a 6-month-old child were less dense and became normal after 5 months' treatment with thyroid extract. Biopsies from the iliac crest before treatment showed primitive bone without differentiation into cortex or medulla. After treatment biopsy showed normal osteoid tissue around the primitive chondroid axis approaching normal bone structure. Jeune & Muller (1959) point out that sclerosis has been recorded with wide variations in the serum calcium and they, therefore, suggest that hypersensitivity to vitamin D, with increased calcium absorption is responsible for sclerosis in hypothyroidism. The renal insufficiency suggested by the raised blood urea was not considered.

Case 5

M.S. Born 31 May 1960. Admitted aged 2 years weighing 10 lb. Temperature 96°F . X-ray showed a wide fontanelle and sclerosis of the skull and wrists (Fig. 6a and c). No carpal centres were seen. Chest X-ray and intravenous pyelography showed increased skeletal density but no other abnormality (Fig. 6b). The centres for femoral heads had not appeared. The serum calcium was $12.5 \text{ mg}/100 \text{ ml}$, blood urea $69 \text{ mg}/100 \text{ ml}$. The hypothyroid state was confirmed by a serum protein bound iodine of $2.7 \mu\text{g}/100 \text{ ml}$.

Thyroxine therapy led to clinical improvement but the child later died from bronchopneumonia. X-rays taken after death showed marked reduction in bone density. Necropsy revealed a hypoplastic thyroid. No renal lesions were found.

Idiopathic osteopetrosis (Albers-Schönberg disease)

In this condition the normal lamellated pattern of cortical and cancellous bone is replaced by dense structureless tissue. Allowing for filling-in of the marrow spaces with bone, the calcium and phosphate content relative to the organic matrix is not significantly increased. The ab-

FIG. 6. M.S. Cretin (aged 2 years). (a) Sclerotic metaphyses and delayed ossification at wrist. (b) Pyelogram showing skeletal sclerosis. (c) Skull showing increased density and delayed closure of fontanelles.

FIG. 7. M.G. Idiopathic osteopetrosis. (a) and (b) Increased density of all bones with periosteal thickening. (c) Skull, increased density especially of base.

normality lies in the arrangement of collagen fibres and in the distribution of mineral salts. Rubin (1964) demonstrated a persistence of the primitive spongiosa but the reason for this is not known. Failure of osteoclastic activity is not solely responsible, as areas of bone resorption occur (Enticknap, 1954; Engfeldt, Engstrom & Zetterstrom, 1954). High urinary phosphate excretion in their cases suggested an associated metabolic disturbance (Pincus, Gittelman & Kramer, 1947) but might have been accounted for by coincident rickets. Dent, Smellie & Watson (1965) note that the condition is inherited as if determined by an autosomal recessive gene. They suggested that, as well as a defect in osteoclasia, there exists an inborn error of metabolism which allowed excessive absorption of calcium across the placenta and gut. They obtained some response by limiting calcium absorption but apparently calcium could not be rapidly released from bone and tetany developed as the serum level fell.

The radiological picture is of dense structureless bone with obliteration of the medullary canal. The bone shafts are more completely affected than in renal osteodystrophy or hypercalcaemia but layers of less dense bone may be seen. The side effects depend on:

- (i) Vulnerability to traumas and infection.
- (ii) Anaemia and compensatory extramedullary haemopoiesis.
- (iii) Pressure on nerves in the narrowed foramina.

Case 6

M.G. Born 18 September 1961. Admitted in January 1962 with a history of failure to thrive, anaemia and feeding difficulty. X-ray showed increased density and periosteal stripping of ribs, shoulder-girdle and long bones (Fig. 7a and b). The metaphyses were fragmented and wrist centres were delayed. Blood calcium, phosphate and alkaline phosphatase were normal. Hb 11.2 g/100 ml, leucocytes 27,650/mm³. Biopsy from iliac crest showed hypoplasia of all elements. The haemoglobin level gradually fell to 7.1 g/100 ml 6 weeks later. The fall was accompanied by the appearance of subperiosteal haemorrhages on X-ray which calcified well and seemed to contribute to the 'os-in-os' appearance at the bone ends. The films resembled those of Back & Cole (1958) in which osteopetrosis was complicated by rickets and scurvy. The nutritional state was good and rickets or scurvy were not considered likely on clinical grounds. The bleeding tendency was attributed to defective haemopoiesis. After transfusion the haemo-

globin level remained at about 12 g/100 ml. The skull (Fig. 7c) became increasingly sclerotic. The feeding difficulty was relieved by insertion of polythene tubing through the blocked posterior nares and the child was allowed home.

Differential diagnosis of increased bone density

It is important to establish that the increase in bone density is real and not an effect of contrasty film quality. Where the appearance of the spine is suggestive of sclerosis, confirmation should be sought at the bone ends. The diffuse density of neonatal bone, exaggerated in erythroblastosis, can be recognized by the history. Rubellar osteitis causes sclerotic foci at the bone ends and is accompanied by erosions and by other features of the syndrome. Idiopathic osteopetrosis must be distinguished from pycnodysostosis (Maroteaux & Lamy, 1962) where bone modelling is normal in spite of increased density, and there is associated hypoplasia of the facial bones with delayed closure of the fontanelles. The bones are short, in particular the distal phalanges, otherwise the general outlook is good on this condition.

When hypothyroidism is responsible for the sclerosis gross delay in ossification will make this clear, but less marked retardation may accompany other causes of failure to thrive.

In many cases there may be an interplay of factors causing osteosclerosis which cannot be sorted out by X-ray findings alone. For example sclerosing renal osteodystrophy may be in part an overcompensated healing of 'osteitis fibrosa generalisata' or of malacia (Reifenstein, 1957; Lalli & Lapides 1965). Toxic action on the osteoclasts would seem a reasonable contributory cause, since the high concentration of calcium developing in such cases would presumably have the same action on bone growth as in idiopathic or nutritional hypercalcaemia.

Similarly when other causes of hypercalcaemia lead to renal failure, the ensuing sclerosis may arise from both these factors. Identifiable subperiosteal erosions may point to a renal origin. It was noted that the cases of hypercalcaemia and sclerosing osteodystrophy came from limestone areas, and not from the city which provides most of our X-ray material.

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