HYPOPHOSPHATASIA

BY

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The purpose of this paper is to describe the histological findings in two cases of congenital hypophosphatasia. Of the two cases, the second was diagnosed only in retrospect and without biochemical confirmation.

In 1948 Rathbun described a generalized disease of bone which was associated with hypophosphatasia, hypercalcaemia and a renal lesion. To this he gave the name 'hypophosphatasia'. Since then other cases have been reported under various names both here and abroad (Engfeldt and Zetterström, 1954; McCance, Fairweather, Barrett and Morrison, 1956; Schlesinger, Luder and Bodian, 1955). From the cases described it is possible to build up a composite clinical picture of this rather bizarre condition. The usual presenting feature is a failure to thrive in the early months of life associated with vomiting and constipation. Biochemically the most significant finding is the virtual absence of the enzyme alkaline phosphatase. In addition there is hypercalcaemia, and renal damage has been found at necropsy providing yet another condition associated with renal calcinosis.

Rathbun's case differs from others so far recorded in the literature in being much younger. The age at death of his patient was 2 months. This may be the explanation of the clinical finding of an almost uncalcified skull. He described the head of this infant as resembling a balloon filled with water. It was this description which suggested the diagnosis in the first of the two cases about to be described.

Case Reports

Case 1. This was a boy, born of healthy parents and with two healthy older siblings. After an uneventful pregnancy the child was delivered by low forceps under general anaesthesia. He was cyanosed at birth but this cleared within a few minutes. Thereafter he had repeated cyanotic attacks and vomited the sugar and water which he was given. When seen on the second day of life the most striking feature was the apparent absence of bone in the vault of the skull. Small plaques of bone could be felt in the occipital and frontal regions, while the rest of the cranium felt like the water-filled balloon described by Rathbun. The spleen was palpable one

fingerbreadth below the costal margin and the liver two fingerbreadths. No other abnormality was found on clinical examination. The child was admitted to the Royal Hospital for Sick Children, Glasgow, on the second day of life. He had repeated convulsions poorly controlled by sedatives and died at the age of 15 days.

X-RAY APPEARANCES. There was defective ossification of the skull and delayed dentition (Fig. 1). The ribs were flared at the costochondral junctions. The metaphyses of the long bones were irregular and pathological fractures of the shafts with some stippling of the epiphyses were observed.

BIOCHEMICAL FINDINGS. The serum calcium level was 18.5 mg./100 ml.; alkaline phosphatase, less than 1.5 K-A units/ml. (three estimations); non-protein nitrogen, 55 mg./100 ml. Post-mortem estimation of

FIG. 1.—Case 1: Radiograph of the skull showing defective calcification.

alkaline phosphatase in the lower end of a humerus yielded 140 K-A units/kg. The average recorded range in the absence of obvious bone disease, and depending upon the site and activity of the growing bone, is 580 to 12,000 K-A units/kg. (Rathbun, 1948).

Necropsy. The body was of average development for a 15-day-old infant and weighed 3.1 kg.

HEAD. The skull felt soft over the vertex, and when the skin was reflected the parietal bones, the posterior aspect of the frontal bones and the anterior aspect of the occipital bones were cut easily with scissors. The base of the skull and the mandible appeared normal. The brain which, weighed 423 g., was removed and sectioned; no lesion was recognized. The venous sinuses were normal.

THORAX. The thoracic contents showed no abnormality. The thoracic cage, however, presented abnormalities at the costochondral junction of the third to tenth ribs on each side. The end of the bone was broadened with an apparent excess of cartilage giving a swollen, wrinkled junction over 1.5 cm., thereafter becoming the normal flattened cartilage articulating with the sternum which itself was normal. The vertebral bodies were smaller than usual but of normal shape. The heads of the ribs were normal. The thyroid gland and paratracheal tissue were carefully dissected and no evidence of parathyroid enlargement was seen.

ABDOMEN. The abdominal contents were substantially normal: in particular, no renal lesion was recognized.

Histology. The lungs, heart, trachea, thyroid, parathyroid, salivary glands, pancreas, spleen, pituitary and testes were examined and showed no significant departure from the normal. An occasional small cast was seen in the cortical tubules of the kidney but no histological evidence of disease was recognized.

THE SKELETON. The following bones were taken for histological examination: ribs, humerus, radius, ulna, femur, tibia, fibula, lumbar vertebra and frontal bone. All blocks were decalcified by the ion-exchange resin method, cut and stained by the picro-Mallory method. All showed lesions, varying only in extent with the individual bone, and the most remarkable were found in the ribs. Here the picture was a grossly distorted metaphyseal line with complete loss of alignment of the columns of cartilage and an irregular pattern of osteoid deposition. Next to the osteoid, a band of bone ran across the rib with another zone of osteoid on the shaft side (Fig. 2). All the ribs examined showed this general picture. Under higher magnification the main features identified were those of a rachitic lesion, namely, the excessive osteoid formation, the development of compression of the cartilage cells at the cartilage-shaft junction and the invasion of the cartilage by capillary loops. The main feature, however, which distinguished this lesion from that of active rickets was the band of bone between the layers of osteoid.

By contrast, an example of a minimal and presumably early lesion could be obtained from an examination of the distal end of the fibula (Fig. 4). Here the metaphysis

was abnormally broad and the cartilage dipped into the shaft at irregular intervals. The osteoid was increased in amount and deposition of bone was variable. Evidence of early compression of cartilage cells could be seen.

The lesion was not always observed throughout the breadth of the metaphysis. As in the upper end of the femur on the medial aspect (Fig. 6), it was often local. In the bones examined this type of local lesion was always subcortical in position. The remainder of the metaphysis was normal as was the spongiosa.

In normal controls of the same age the proportion of osteoid to bone was found to be variable, the most constant feature being the regularity of the alignment of the spongiosa. Thus in both the grades of lesion described the spongy bone of the shaft was uninformative except in that the spicules of spongy bone in the ribs examined were much thicker and better ossified than in the normal controls. This is in contrast to the picture seen in active rickets.

Similar lesions were found at the lower ends of both femur and fibula. In addition, the fibula showed a lesion which was confined to the shaft (Fig. 5). Here a band of osteoid and poorly calcified bone traversed the shaft about 15 mm. from the metaphysis. This appeared to be a healing fracture and the deficiency of cortical bone at this point strongly suggested an intra-uterine origin.

Even at this early age of 15 days, evidence of some healing could be found. Such an example was seen in the head of the radius (Fig. 3) where there was bone deposition on irregular columns of cartilage cells. As in rickets the phases of osteoid production and ossification may thus occur together. There were, however, some examples also of broadening of the cartilage with no attempt at ossification as in the distal end of the ulna. Thus repair lacked uniformity and varied with the individual bone. A lumbar vertebra was examined and bone formation found to be within normal limits.

At a higher magnification it can be shown that in normal controls the osteoblastic reaction does not surround every spicule and that even where bone is being laid down most actively, namely, near the metaphysis, the presence of osteoblasts is inconstant. Thus an evaluation of osteoblastic activity can only be made by examining a considerable extent of bone. In the ribs of this case there was no doubt about the presence of osteoblasts around some of the osteoid at the metaphysis (Fig. 7). Osteoblastic activity was also demonstrable in the bone scar and the adjacent cartilage (Fig. 2). Periosteal deposition of bone was active as estimated by the number of osteoblasts (Fig. 8), where there was also an excessive deposition of osteoid. Osteoclasts were very seldom found in association with the spongiosa although they were occasionally seen in periosteal bone.

Even in the mild lesion as in the lower end of a fibula, the irregularity of bone deposition on the spongiosa was clearly demonstrable, while the osteoblastic reaction round these spicules was within normal limits. Where the bone had fractured the osteoblastic response was good and evidence of bone modelling was recognized by the occasional presence of osteoclasts. In the fracture of the lower end of fibula the osteoid was young and

FIG. 2.—Case 1: Rib, picro-Mallory $\times 12$.

FIG. 4.—Case 1: Fibula, picro-Mallory $\times 12$.

FIG. 3.—Case 1: Radius, picro-Mallory $\times 22$.

FIG. 5.—Case 1: Fibula, picro-Mallory $\times 22$.

FIG. 6.—Case 1: Femur, picro-Mallory $\times 12$.

FIG. 8.—Case 1: Rib, picro-Mallory $\times 95$.

FIG. 7.—Case 1: Rib, picro-Mallory $\times 260$.

FIG. 9.—Case 1: Parietal bone, picro-Mallory $\times 180$.

more actively laid down in the spongiosa than in the cortex, where there was actually a gap in the bone (Fig. 5). At the head of the radius where the metaphyseal lesion was more advanced in repair than in any other bone examined, the osteoblastic activity was good. Here again there was a slight increase in connective tissue.

Osteoblastic activity was more marked in the calvarium than in any bone examined. The outer table was poorly ossified but the inner table was more normal in density. It would appear that the defect is in the actual deposition of calcium. Certainly all the cellular components were present (Fig. 9) and the architecture of the membranous bone was within normal limits.

Case 2. This was a boy, born of healthy parents. He was the fifth child in the family and only one other child survived. In one, who had died almost immediately after birth, the diagnosis of achondroplasia had been made elsewhere. The history of the present case was that he appeared healthy at birth but after the first month he vomited intermittently, took his feeds poorly and failed to thrive. At the age of 6 weeks he was found to have widespread bony deformities and the skull sutures were widely separated. At this time a diagnosis of polyostotic dysplasia was made. He was first admitted at the age of 6 months with acute diarrhoea and vomiting and died the following day before any investigations could be carried out.

X-RAY APPEARANCES. In the light of new information

FIG. 12.—Case 2: Kidney, Von Kossa $\times 4\frac{1}{2}$.

the films of this child who died in 1950 were re-assessed by Dr. S. P. Rawson who suggested a revised diagnosis of hypophosphatasia.

SKULL. There was deficient mineralization of bones forming the vault of the skull with wide sutures and enlargement of the fontanelles. The base of the skull was also affected to a lesser degree.

LONG BONES. There was deficient mineralization with abnormal patchy calcification of the metaphyses which show irregular zones of proliferative cartilage, enlargement of the epiphyses and an increase in width of the epiphyseal cartilage. The long bones were bowed from deficient bone structure.

RIBS. There was some decalcification with expansion and flaring at the outer ends at the costochondral junctions.

Necropsy. The body was that of a rather thin male infant weighing 3.4 kg., this being only half his expected weight. The upper and lower limbs were misshapen, in that they were bowed outwards and were shorter than the average. The bones of all four limbs were removed and examined.

SKULL. The fontanelle was large and the frontal bones were not as well ossified as one would expect at this age.

ALIMENTARY SYSTEM. There was nothing of note apart from a considerable fatty change in the liver.

GENITO-URINARY SYSTEM. The left kidney weighed 33 g. and the right 30 g. Both organs were congested, the medulla more so than the cortex. At the boundary zone of the medulla were numerous streaks of a crystalline deposit: these proved to be calcium (Fig. 12). Pelvis, ureters and bladder were normal.

THORAX. The contents of the thoracic cavity revealed no abnormality of note.

Histology. The lungs, heart, pancreas, spleen, adrenal, pituitary, cerebellar cortex, cerebral cortex and marrow were examined and showed no significant lesion.

LIVER. There was moderate fatty change with considerable intracellular pigment in the periphery of the lobule.

THYMUS. Some small centres of erythropoiesis were seen in the septa.

ILEUM AND COLON. There was lymphoid hyperplasia with some infiltration of inflammatory cells into the villi, indicating a degree of enteritis.

KIDNEY. Each kidney showed a considerable degree of medullary calcinosis with a few small focal lesions in the cortex as well. The medullary lesions consisted of discrete granulomatous patches with granular degeneration, variable in size and characteristically situated in the outer medullary zone. The patches contained a variable amount of calcium stainable by Von Kossa's method (Fig. 12). One may presume that these would obstruct the tubules and cause subsequent dilatation. The granulomata probably originate both in and between the tubules.

The histological picture conforms to the description of nephrocalcinosis by Rhaney and Mitchell (1956).

SKELETON. The following bones were available for examination: humerus, radius, ulna, tibia, fibula and both femora. All showed a similar lesion. At the distal end of the right tibia (Fig. 10), the thickened line of cartilage was clearly seen and into this grew loops of capillaries, a feature indistinguishable from rickets. Equally evident was the broad line of densely ossified cancellous bone on the shaft side of the capillary loops. This band was constant at the ends of all long bones examined. At a higher magnification (Fig. 11) the collapse of columns of cartilage cells could be seen between the invading capillary loops. Osteoblasts were numerous. Their presence was most marked at the cortex and in the band of bone next to the metaphysis where osteoclasts were also seen. The spicules of the spongiosa were smaller than normal so that for some distance on the shaft side of the dense metaphyseal band the medullary bone was more rarified (Fig. 10). Nevertheless the ossification within the shaft was normal. There seemed to be little attempt at bone modelling here as osteoclasts were scanty.

FIG. 10.—Case 2: Tibia, picro-Mallory $\times 4$.

FIG. 11.—Case 2: Tibia, picro-Mallory $\times 12$.

Discussion

The diagnosis of the first case can hardly be called in question; apart from the close clinical resemblance to Rathbun's case, the extremely low figures for alkaline phosphatase both in blood and bone must be regarded as conclusive. The diagnosis of the second case, on the other hand, must remain to some extent presumptive. Nevertheless the clinical and radiological picture is sufficiently close to make such a diagnosis a reasonable assumption. To add to this there is a similarity in the histological appearances of the bones of both these cases which outweighs the differences, especially as the latter may well be due to the difference between their ages at death.

The radiological picture itself is sufficiently distinctive to suggest the diagnosis. The combination of multiple fractures and grossly defective ossification of the skull is highly suggestive; indeed the picture shown of the skull in our first case (Fig. 1) is probably pathognomonic.

In assessing histological deviations from the normal we have kept in mind the possible variation which may be found unassociated with disease. For this reason a number of samples of ribs at the costochondral junction were examined from children of

the age of 14 days who had died from causes not related to bone disease or disorder of calcium metabolism as far as was known. It was apparent that at this age there was considerable variation in the extent of the ossification of the spongiosa and of the osteoblastic activity associated with it. The normal regularity of the metaphyseal line, however, was constant.

Samples of other generalized disorders of bone were also examined for purposes of comparison. The features of osteogenesis imperfecta and achondroplasia differed so considerably from our own two cases that detailed comparison is unnecessary.

Classical rickets presented more of a problem. In the first place, other writers have used the term rickets for this disease as it affects the older child in whom metaphyseal changes are radiologically more marked while changes in the skull are less (Schlesinger *et al.*, 1955).

Secondly, whereas a fair comparison might be made between classical rickets and our second case, this was not possible in the case of an infant only 2 weeks old. Nevertheless, in both cases some of the salient features of rickets were apparent. There was broadening of the metaphysis with an increase in osteoid tissue and irregular bone formation, invasion of the cartilage by capillary loops and compression of the columns of cartilage cells (Park, 1939). The differences are, perhaps, more remarkable than the similarities. Most noteworthy is the presence of the metaphyseal band of bone running through the osteoid seen in our cases. Moreover, and this is seen most markedly in our second case which might otherwise be regarded as more closely resembling rickets, there is the combination in the same section of signs of activity (invasion of capillary loops) and signs of healing (bone formation). Minor differences from rickets are the multiple spontaneous fractures, the rarity of osteoclasts, and the well-ossified spicules of the spongiosa.

In this connexion it must be remembered that in any specialized tissue the possible reaction to disease must inevitably be limited by its structure. It is likely, therefore, that any interference with the normal ossification process of the growing bone will result in a somewhat similar histological picture. There are already described various kinds of rickets such as renal rickets, resistant rickets and others with causes ranging far from the original concept of a vitamin deficiency. On this analogy it might well be possible to include hypophosphatasia as yet

one more example of 'rickets'. There is a danger, however, in degrading the term 'rickets' with its relatively clear-cut pathogenesis into a generalization including all disorders of ossification. The advantage of the term hypophosphatasia lies in its emphasis upon an important diagnostic feature and moreover brings it into line with the current concept of familial enzymatic deficiencies to which the disease probably belongs (McCance *et al.*, 1956).

It remains to consider the term 'osteoblastic dysplasia' introduced by Schlesinger and his colleagues (1955). In neither of our cases could such a view be sustained; the variability of osteoblastic activity in the normal was found to be such that the usual bone biopsy must be regarded as inadequate for its assessment.

The presence of nephrocalcinosis in a condition associated with hypercalcaemia is not unexpected. It is tempting to see its gradual development during the course of the disease at different ages. In our first case dying at the age of 2 weeks there was no obvious renal damage. In Rathbun's case dying at 2 months there was a renal lesion without calcinosis, while in our second case dying at the age of 6 months the complete lesion of medullary nephrocalcinosis could be demonstrated.

Summary and Conclusions

Two cases of congenital hypophosphatasia are described, the second case being a presumptive diagnosis based upon clinical, radiological and post-mortem findings. Detailed histological examination of the skeletons in both cases showed many of the histological features of rickets. Nevertheless, the whole picture differs considerably from that disease. Some of the clinical and radiological variations described in the literature are probably associated with the differing ages at death of the cases described. No evidence was found for regarding hypophosphatasia as an osteoblastic deficiency.

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