A CASE OF OSTEOSCLEROSIS WITH HYPERCALCAEMIA AND RENAL FAILURE

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(RECEIVED FOR PUBLICATION DECEMBER 10, 1956)

Disorders of calcium metabolism in childhood (except rickets) were regarded as uncommon until the recognition by Lightwood (1952) of the syndrome of 'idiopathic hypercalcaemia of infants with failure to thrive'. Previously there had been occasional reports of children considered to have Albers-Schönberg disease, hypervitaminosis D, primary hyperparathyroidism (Pratt, Geren and Neuhauser, 1947; Philips, 1948) and hyperparathyroidism with renal disease (Andersen and Schlesinger, 1942).

Albers-Schönberg disease is generally regarded as not causing hypercalcaemia, renal damage or ectopic calcification, but these may occur in the other conditions.

Some of the patients described in the literature do not apparently belong to any of these groups. For example, Lightwood (1932) reported a dwarf with mental retardation, osteosclerosis, calcinosis, arterial degeneration and renal damage. Butler (1951) described a similar condition.

Idiopathic hypercalcaemia is regarded by some as occurring in both mild and severe forms, though the latter may be a separate syndrome (Lightwood and Stapleton, 1953). There are patients who show only some of the features of the fully developed severe form and there appears to be a continuous spectrum between the extremes. It is possible that some of the cases described in the older reports were examples of the severe form, and the same is true of this patient.

Case History

L.B.G.H. (No. 11038), a boy, born on September 28, 1952, was admitted on August 6, 1955, aged 2 years 10 months.

The family history was not remarkable; there was one healthy sibling two years older than the patient. His mother had taken the usual supplements during her pregnancy, and delivery was normal at full term.

Except for feeding difficulties and an unusual diet the child developed normally until his final illness. He had bronchitis at the age of 3 months but this soon resolved.

He sat up and also cut his first tooth at 7 months and started to walk and talk at 19 months. A photograph of the child at 2 years of age shows a chubby normal infant.

At 2 years 9 months he contracted whooping cough. He lost about 4 kg. in weight during the acute phase, and after the cough subsided his appetite remained very poor and weight loss continued. He complained of itching of the skin, became pale and lethargic, and his parents noticed that he had frequency of micturition. He was constipated.

Six weeks after the onset of the whooping cough a left facial palsy was observed and he was admitted to hospital.

Dietary History. He was breast fed from birth for four weeks, when he was changed to half-cream dried milk because the breast milk failed. At 10 weeks he was changed to full-cream milk.

At 4 months weaning was attempted but he refused all solid foods, and vomited if these were pressed. At 6 months he was persuaded to take a little solid carbohydrate and strained vegetable foods, but at 8 months again refused to take these and continued to exist solely on milk. At 1 year of age he was changed from full-cream dried milk to tuberculin-tested pasteurized cow's milk, and he lived almost exclusively on this for the rest of his life. During the year before admission he had been taking about 3 pints of milk a day. He had been known to take on occasions minute amounts of baked beans, apple, banana, chocolate, toast and butter. He had always refused Ministry of Food orange juice, but had a very occasional teaspoonful of cod liver oil.

On examination, his height was 89 cm. (ideal height for age, 95 cm.), his weight 11.5 kg. (ideal weight for age, 14.6 kg.) and the circumference of the head 50 cm. (normal). He was afebrile. The pulse rate was 110-130/min.

Appearance. His face (Fig. 1) was thin and the forehead was prominent. The muscles were wasted and the skin-fold thickness over the biceps was only 3.0 mm., indicating an almost complete disappearance of subcutaneous fat. The skin was dry and lightly pigmented and showed numerous scratch lesions. There was an obvious weakness of the left side of the face and this

fluctuated considerably from day to day, being sometimes almost absent.

Intelligence. The level of intelligence was good. Formal testing could not be undertaken because of the child's condition, but there was no evidence of mental deficiency; in fact, the general impression was that the child was in advance of his chronological age. He was able to speak quite well, though his voice was husky and he talked little. He knew about 20 letters of the alphabet, and recognized familiar fairy tales.

Temperament. The boy was difficult to manage, rarely smiled, and cried easily. He was most reluctant to take any food but drank water avidly.

Systematic Examination. The tongue was dry and all the deciduous teeth were present and though worn were not carious.

No abnormality was found in the chest.

The pulse was regular. Blood pressure by auscultation was 190/100 mm. Hg. The heart was enlarged and there was a harsh apical systolic murmur. The peripheral vessels were easily palpable and stony hard to the touch at wrists, elbows, groins and knees.

No abnormality was found in the abdomen.

A left lower motor neurone facial palsy was present. There was a bilateral plastic iritis and the optic fundi showed a hypertensive retinopathy.

Investigations on Admission. A blood count gave: Haemoglobin 6.8 g. %, M.C.H.C. 27.2 %, M.C.V. 78 cubic microns, white cell count 5,500/c.mm. (neutrophils 47%, lymphocytes 50%, eosinophils 3%). Polychromasia was greater than normal and there was some punctate basophilia.

The serum calcium level was 12 mg. % (on two occasions) and serum phosphorus 8.5 mg. %. Blood urea was 133 mg. %. The serum sodium level was 134 mEq./litre, serum potassium 4.3 mEq./litre and serum chloride 92 mEq./litre. The serum bicarbonate level was 15 mEq./litre, serum cholesterol 329 mg. %, serum albumin 4.15 g. %, serum globulin 3.95 g. % and alkaline phosphatase 19 units (King-Armstrong). Electrophoresis showed a small increase in the γ globulin, and a more marked increase in the α_2 and β globulins.

Lumbar puncture and cerebrospinal fluid were normal. The blood Wassermann and Kahn reactions were negative. The urine contained a trace of albumin, a few

leucocytes and *E. coli* was recovered on culture. The urinary amino-acid excretion was normal.

Radiographs. The whole skeleton was hypercalcified. The ribs were uniformly opaque whereas the iliac crests showed numerous narrow concentric bands of increased density (Fig. 2). The base of the skull was thickened and there was no remodelling in the femoral shafts. In the metacarpals and phalanges there was a well-marked transverse line of increased density 1-2 mm. wide. Next to it on the epiphyseal side was a similar zone of normal density and then the rest of the bone to the epiphysis was of slightly increased density (Fig. 3).

The position of the dense line was such that it would have been next to the epiphyseal plate at the age of 12 to 18 months. This is the time these epiphyses appear. There were no longitudinal striations in the phalanges.

Calcification of the femoral arteries was visible for the whole length of the thighs and at the knees (Fig. 4). Epiphyseal development was within normal limits.

Electrocardiograph. This showed sinus rhythm and depression of S-T segments in leads V.3 and V.6. Corrected Q-T interval was 0.475 sec. (prolonged). It was considered that these changes could be due to the high serum calcium level.

Progress. A low-calcium diet was started at once, and because of the acidosis oral alkali therapy was given. After three days the serum bicarbonate level was

FIG. 1.—Patient aged 3 years.

FIG. 2.—Radiograph of the abdomen.

FIG. 3.—Radiograph of the hand.

36 mEq./litre, so the alkali was stopped, but the low-calcium diet was continued for the rest of the patient's life (for intake see Fig. 5).

After one month in hospital the child was a little better. His weight, however, had not risen, but the plastic iritis had improved with local cortisone. It was found that there was rather more pus in the urine, and a course of oxytetracycline was given. The serum calcium had fallen to 11 mg. %, and the blood urea was 180 mg.%. The serum bicarbonate had fallen slowly to 20 mEq./litre.

At the end of the second month there was further improvement, with a gain in weight of 1 kg., though feeding was a perpetual difficulty and three or four hours a day were spent in coaxing scraps of food into the child. Pruritus was troublesome.

The blood pressure was higher, around 240/130, on repeated estimations (by auscultation). The creatinine clearance on two estimations was 2.0 and 2.4 ml./min. Serum calcium was 11 mg. %, the blood urea was 204 mg. %, the serum bicarbonate had fallen to 15 mEq./litre and the serum phosphorus was 8 mg. %. The anaemia was unchanged despite treatment with oral and intramuscular iron.

Balance Studies. The child's condition did not permit continuous urine collection, but several timed samples were obtained and 24-hour excretions calculated from them. The urine calcium estimated in this way varied from 13 to 21 mg./day.

All the stools were analysed over a 10-day period, and it was found that the calcium balance was minus 33 mg. per day.

Cortisone therapy was tried in cautious doses, with a maximum of 15 mg. a day, for three weeks. There was no clinical effect observed but the faecal calcium became even lower during this time, and consequently the cortisone was stopped.

At the end of the third month the child was evidently worse. His weight was falling, and feeding was becoming even more difficult. Serum calcium was 9.8 mg. %, phosphorus 9 mg. %, blood urea 230 mg. %, serum bicarbonate 10 mEq./litre, and serum potassium 3 mEq./litre. Haemoglobin was 3.5 g. %.

Several small blood transfusions were given, and the haemoglobin was raised to 6.0 g. %, with slight improvement in the patient's condition. About this time he developed persistent diarrhoea, for which no infective cause could be found, and various oral electrolyte supplements were needed.

During the fourth month persistent vomiting made it impossible to maintain nutrition and he wasted rapidly. Later, fluid intake was also inadequate, and he became

FIG. 4.—Radiograph of the thighs.

dehydrated. Electrolyte solutions were given subcutaneously and intravenously and the dehydration was corrected, but oliguria then developed and the child died a few days later.

Necropsy. Necropsy was performed by Dr. K. Thompson.

Externally the body was that of a slightly oedematous male infant. The right testis was in the inguinal canal, the left in the scrotum.

The heart was enlarged, due to hypertrophy of the left ventricle. There were no valvular defects or septal deficiency. The lungs were oedematous; there was no evidence of purulent infection of bronchi or trachea. The aortic valvular ring was calcified and there was patchy calcification of the wall of the aorta throughout its length, which calcification continued up the carotid arteries and down the iliac arteries into the femoral arteries. No parathyroid bodies were identified.

The liver was enlarged and oedematous, being of a pale buff colour. There was no abnormality in the spleen. Both kidneys were shrunken, the left kidney being less shrunken than the right. The cut surfaces of the kidneys showed blurring of the demarcation line

between cortex and medulla, with considerable prominence of the vessels. There was patchy calcification which was both visible to the eye as well as grating to the knife. The renal tissue was oedematous and focally mottled with purple congestion against a grey background, the scarred contracted cortices being irregularly nodular. Both suprarenals showed abundant grey medulla, a clear distinct pigment zone and abundant firm yellow cortex. There was oedema of the stomach and intestines. The stomach contained mucus and streaks of altered blood.

In the head, the brain was oedematous. There was very marked thickening of the base of the skull, particularly of the sella turcica. The tentorium cerebelli contained plaques of calcium forming a rigid sheet in the anterior part.

THE SKELETON. In the ends of the ribs there was no irregularity or excess of the proliferating cartilage. The yellow zone of the provisional zone of calcification was less than 0.5 mm. wide and straight, and no abnormality in the bone structure could be seen. In the lower end of the femur the growth line was irregular, the zone of provisional calcification being wide and irregular and

FIG. 5.—Chart of calcium intake and serum analyses.

there being grey 'epiphyseal' lines showing as ghosts against the purple marrow at the lower end of the shaft. In the iliac crest the bone was in part grey and apparently avascular and in part purple and congested, giving a very mottled appearance to the eye and cutting irregularly to the knife.

Histology. Histological sections were examined by Dr. D. B. Brewer:

KIDNEY. The kidney tissue (Fig. 6) is virtually destroyed. The outer part of the cortex is grossly shrunken. Every glomerulus in this area is completely hyalinized and almost every one is calcified. They are crowded close together. No normal tubules are present. Between the glomeruli are tubules of narrow lumen lined by small cells with dark round nuclei. They resemble closely foetal tubules and in one or two areas are proliferated to form papillary projections into a dilated cyst-like tubular lumen.

There is an irregular zone of cortex which is less affected. There are present here a few normal glomeruli

FIG. 6.—Photomicrograph of outer cortical zone of kidney. ($\times 45$. H. and E.)

FIG. 7.—Photomicrograph of iliac crest bone. ($\times 23$. H. and E.)

but the majority show capsular adhesions with epithelial proliferation about them. Some of these glomeruli are partly hyalinized and one or two show patchy calcification. The tubules in this zone are dilated and lined by atrophic epithelium. In addition to the calcification of glomeruli there are very numerous irregularly distributed areas of interstitial and intratubular calcification particularly numerous in the medulla. Many of the larger arteries also show fine calcification along the elastic lamina. In the arcuate and smaller arteries there is marked intimal thickening by loose cellular tissue that in many cases almost completely obliterates the lumen. The media in these vessels appears normal and there is no intimal thickening in the large branches of the renal artery in the medulla.

MYOCARDIUM. There is moderate diffuse mucoid oedema of the myocardium, and cellular mucoid thickening of the valve cusp. There is also calcification of the valve ring.

FEMORAL ARTERY. Marked crescentic calcification of the media is seen.

SUPRARENAL. The suprarenal is normal, but all the small arteries in the peri-adrenal fat show a slight deposit of calcium on the internal elastic lamina.

LIVER. The sinusoids are only moderately dilated with widespread fatty change.

BONE (RIB AND ILIAC CREST). Both show similar changes though they are more marked in the iliac crest. There is an excessive amount of cancellous bone which, as a result, has become compact bone in the blade of the ilium. The bone is well formed but the lamellar

structure is interrupted throughout by small, irregular, persisting islands of cartilage (Fig. 7).

Discussion

This patient closely resembles the reported cases of the severe form of idiopathic hypercalcaemia except in three particulars, namely, the absence of the characteristic facies and mental retardation (Schlesinger, Butler and Black, 1956) and the late onset of evident ill health.

The severity of the osteosclerosis and ectopic calcification on admission only six weeks after the whooping cough suggests that the pathological processes were far advanced while the child was apparently well. It would appear from the position of the band of increased calcification in the metacarpals and phalanges and the lack of remodelling in most of the femoral shaft that those processes began when the child was about 1 year old.

During the year before admission, his diet had comprised 3 pints of cow's milk a day, which contains:

Protein	..	..	..	56 g.
Fat	..	..	..	63 g.
Calories	..	..	..	1,120
Calcium	..	..	..	2.0 g.
Phosphorus	..	..	..	1.6 g.
Cholesterol	..	..	..	340 mg.
Vitamin D	..	..	..	17 units
Vitamin C	..	..	..	about 15 mg.
Iron	..	..	..	1.3 mg.

The intakes of fat, protein and calories were well enough balanced but the calcium, phosphorus and cholesterol were about twice the amount in the normal diet of a 3-year-old. At the age of 2, the normal retention of calcium is about 90 mg./day, and this falls to 60 mg./day by the age of 3 (Mitchell, Steggerda, Hamilton and Bean, 1945). The vitamin D intake was very low, while the vitamin C intake was probably adequate.

However, on this diet the child appeared to grow well without mental or physical retardation until his final illness.

The serum cholesterol and calcium levels were raised, though not greatly, and both later fell to normal. The other changes in the serum chemistry can be ascribed to the renal failure. The syndrome known as 'renal tubular acidosis' (Lightwood, Payne and Black, 1953) seems an unlikely diagnosis as a very short course of alkali therapy produced a persistent alkalosis. The serum calcium $\times$ phosphorus product was 101 on admission and never fell below 73. Presumably it was the high product which caused the excessive deposition of bone salts in ectopic sites, and it seems reasonable to suppose that it was also responsible for the osteosclerosis. The mechanism responsible for the latter must have been more complex as the excess bone appears to

be normally calcified osteoid tissue so that the balance of osteoblast-osteoclast activity must have been changed in such a direction as to cause an increase in total bone matrix.

The radiographic changes in the bones resembled those of Albers-Schönberg disease, but the fine longitudinal fissures in the long bones and phalanges (Brailsford, 1953) which occur in that condition were absent. Histological examination of the iliac crest, however, showed persisting islands of cartilage in the excessive cancellous medullary bone such as is seen in the long bones in Albers-Schönberg disease (Warkany, 1954).

Pressure on the facial nerve from expanding bone was presumably the cause of the facial palsy.

The renal lesion was severe and it is not possible from microscopy to form an opinion as to whether chronic pyelonephritis or glomerulo-nephritis might have been present, nor whether the nephrocalcinosis was primary or secondary. The glomeruli of the outer layer of the cortex were nearly all destroyed whereas in the juxtamedullary zone they were less damaged. This differential involvement was noted in a case of severe idiopathic hypercalcaemia described by Lowe, Henderson, Park and McGreal (1954).

The poor response to treatment is not surprising in view of the severe renal damage. A low-calcium diet induced a slight negative calcium balance, which is the usual finding; but small doses of cortisone were accompanied by a fall in faecal calcium (the intake being unchanged), and this is contrary to other reports (Forfar, Balf, Maxwell and Tompsett, 1956).

It is tempting to think that the high calcium and phosphorus product was related to the excessive calcium intake. In the young child, urine calcium tends to be low, and a rise in calcium intake is accompanied by calcium retention (Smith, 1951). It seems reasonable to postulate that calcium retention due to excessive intake might cause an elevation of the serum calcium level of the order which occurred in this case (12 mg. %).

The changes of calcium metabolism in renal failure are usually ascribed to phosphate retention with a secondary fall in serum calcium and consequent failure of calcification of osteoid tissue and secondary hyperparathyroidism. If the serum calcium was kept high as a result of an excessive retention, this sequence might be changed. The high calcium $\times$ phosphorus product would allow normal calcification and the high serum calcium prevent secondary hyperparathyroidism.

In adults, renal failure may occasionally be accompanied by osteosclerosis. Crawford, Dent,

Lucas, Martin and Nassim (1954) reported three such cases and commented on the similarity between them and the severe form of idiopathic infantile hypercalcaemia although in those cases the serum calcium was low.

Renal tract infections are common in idiopathic hypercalcaemia, but it is generally thought that primary renal disease is not responsible for the syndrome.

In this patient, however, it seems quite possible that the renal damage was primary and that the subsequent biochemical changes were modified by the high calcium and phosphorus intake, though it is not possible to determine what was the nature of the original renal lesion.

Summary

A patient is described who, after developing normally for nearly three years while living on milk alone, then died of renal failure. There was hypercalcaemia, hypercholesterolaemia, osteosclerosis, gross ectopic calcification, hypertension and severe renal damage. It is suggested that the aetiology in

this case might be a primary renal disease with the biochemical changes modified by the diet.

I wish to thank Professor J. R. Squire for helpful advice and permission to publish; Drs. V. M. Crosse and F. L. Ker for permission to publish; and Drs. K. Thompson and D. B. Brewer for the necropsy and histological reports.

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