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OSTEOMALACIA IN VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS

METABOLIC STUDY OF A CASE

BY

PAUL D. SAVILLE, M.B., M.R.C.P.

J. R. NASSIM, B.M., F.R.C.P.

F. HARWOOD STEVENSON, M.D., M.R.C.P.

LILY MULLIGAN, B.Sc.

AND

MARGARET CAREY, B.Sc.

From the Royal National Orthopaedic Hospital, London

Von Recklinghausen's neurofibromatosis is a hereditary and familial disease. It is characterized by lesions of skin, nerve, and bone. Skeletal abnormalities are said to occur in 7% of cases (Gould, 1918; Reuben, 1934). The commonest abnormality is scoliosis (Hagelstam, 1946; Fairbank, 1951). There may be overgrowth or undergrowth of individual bones, while neurofibromata may erode the bones from the periosteum or cystic changes may occur in bone.

Apart from neurofibromatous affection of bone, the occurrence of osteomalacia in association with neurofibromatosis has been reported too often to be a chance finding. Gould (1918) reported typical histological findings of osteomalacia in five cases of von Recklinghausen's disease which he examined *post mortem*. He gave no indication of the aetiology. Since then further cases have been reported but without full metabolic investigations. Merklen and Israel (1934) described a case of von Recklinghausen's disease with general rarefaction of bone and Milkman's syndrome. Milkman's syndrome is now generally believed to be invariably due to osteomalacia. Nørgaard (1937) described many radiological abnormalities of the skeleton in two cases. In Fig. 3, Case 1, of his article it can be seen that the *x*-ray film of the pelvis shows a pseudo-fracture through the left inferior pubic ramus and another through the superior pubic ramus. The patient was 22 years old, and an *x*-ray film one year previously showed no pseudo-fracture. This patient then was undoubtedly suffering from osteomalacia. Hernberg and Edgren (1949) reported the case of a woman aged 32 with neurofibromata of skin and multiple pseudo-fractures (Looser–Milkman syndrome). She had a serum inorganic phosphorus of only 2 mg. per 100 ml. with normal calcium, and was given 11 million units of vitamin D in twelve weeks with no apparent effect until eight months later, when healing occurred. They suggested that this might be a "parallel phenomenon" to von Recklinghausen's disease or raised resistance to vitamin D. Since then knowledge of the pathogenesis of osteomalacia and rickets has advanced, and it is now clear that these cases are due to a hereditary abnormality of the renal tubule. Dent (1952) described two cases of osteomalacia in von Recklinghausen's disease which he considered to be due to resistant rickets (Types I and II respectively). Fraser and Nordin (1953) reported a case which they felt was due to resistant rickets. Swann (1954) also reported several cases of this syndrome.

We are recording a further case in which the opportunity was taken to make metabolic studies on varying doses of vitamin D, proving conclusively that this disease falls into the group known as resistant rickets. In addition, biopsies were made from affected bone, and the results of these are also reported.

Case History

The patient was a man aged 55 who for seven months before admission had increasingly severe backache, made worse by coughing and sneezing. More recently he noticed aching pain in his shoulders, left ankle, and left foot. Walking was almost impossible. His general health was satisfactory, but he had always had a "weak bladder" and passed urine every 1½ hours by day, and two or three times at night. He had had no relevant past illnesses, apart from "fits" as a child. His father and paternal grandmother had had neurofibromatosis.

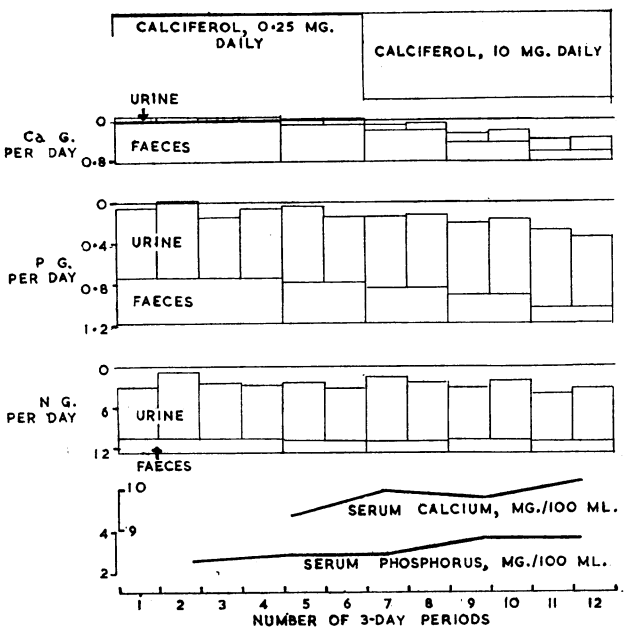
Examination revealed a stunted little man with typical skin lesions, both pigmentation and tumours, covering the trunk, head, neck, and limbs. The right leg was 1½ in. (3.8 cm.) shorter than the left, and all the muscles below the right knee were partially atrophied. There was a tarsal equinocavus deformity of the right foot. He gave the impression of being of rather low intelligence, and was virtually illiterate.

Investigations.—Haemoglobin, 98% (14.5 g. per 100 ml.); W.B.C., 6,750 (normal differential count); E.S.R., 3 mm. (Wintrobe). Urine: normal cytology; sterile on culture, no albumin or sugar. Serum calcium, 9.9 mg. per 100 ml.; phosphorus, 2.2 mg. per 100 ml.; alkaline phosphatase, 14.5 King–Armstrong units; potassium, 5.3 mEq/l.; alkali reserve, 29 mEq/l.; blood urea, 37 mg. per 100 ml.; plasma protein, total 6.9 g. per 100 ml. (albumin 3.2 g., globulin 3.7 g.). Urea clearance, 63% of normal (uncorrected). Glucose-tolerance test, normal, rising from 70 to a maximum of 151 and back to 70 mg. per 100 ml. in two hours. Sugar appeared in the urine at the height of the curve. Paper chromatography of urine: No aminoaciduria; superglycine pattern present, which we have come to associate with osteomalacia in the adult (C. E. Dent). *X*-ray examination showed multiple fractures of ribs ("There is an opacity in the right lower zone which on lateral view is seen to be below the diaphragm, which is tented up over it.") There was some kyphosis and some demineralization of the

spine. "The tibiae and fibulae are markedly porotic. There is a cystic appearance at the upper and lower ends of the left fibula and the upper ends of the tibiae. There is a pseudarthrosis at the lower end of the left fibula, resulting in valgus deformity of the ankle. There are pseudofractures through the lower third of the shaft of the left tibia and neck of right femur." Fat balance: On 80 g. intake there was 93% absorption over twelve days. The patient required four daily doses of 700 mg. of ascorbic acid orally before he was "saturated."

Pathological Report.—Biopsy specimens were taken from the left femur and left fibula, including the pseudarthrosis, and also a chip from the tibia in the region of the pseudofracture, three months after treatment. *Resected portion of fibula:* The specimen consisted of a length of fibular shaft approximately 2 in. (5 cm.) in length. The upper part was reasonably normal in its external appearance, while the lower part was irregular in contour and ended as one surface of a pseudarthrosis. Histologically the lower part of the bone was extremely osteoporotic, and its periosteal surface was deeply indented by irregular masses of mucoid fibrous tissue. Degenerated cartilage and fibrocartilage covered the surface of pseudarthrosis. The upper part of the bone was slightly osteoporotic: excessive amounts of osteoid tissue could not be demonstrated in either situation. *Biopsy from tibia:* Sections showed that the localized rarefaction evident clinically at the site of biopsy (an "Umbauzone" of Looser) was the result of resorption of bone. Haversian spaces were greatly enlarged: there was some irregular new formation of bone, including some periosteal new bone. There was no evidence of excessive amounts of osteoid tissue on the surface of either the compact or the trabecular bone.

Metabolic Procedure.—The patient was admitted to the metabolic ward at the country branch of the Royal National Orthopaedic Hospital. He was not confined to bed, but allowed to sit in a chair. The metabolic regime and the collection of excreta followed the methods advocated by Albright and Reifenstein (1948). Urine was collected in three-day and faeces in six-day periods. Food was prepared by the dietitian in the metabolic unit kitchen. Bulk supplies of meat, biscuits, and homogenized milk were used. Bread was made in the unit from unfortified flour.



In these metabolic charts the intakes are measured vertically downwards from the baseline marked O. Positive balance is indicated by the fact that the rectangles showing urinary and faecal output fall below this baseline—that is, excretion is less than intake; and negative balance when they reach above the baseline—that is, excretion is greater than intake.

Distilled water was used throughout. The diet was analysed twice during the balance. The patient was on this diet eight days before balance studies were recorded.

The diet contained; calcium, 813 mg. per day; phosphorus, 1,184 mg.; nitrogen, 12.55 g. Three litres of distilled water was given daily. Balance data for calcium, phosphorus, and nitrogen for six consecutive six-day periods are shown in the Chart. The following points will be noted:

Six-day Periods 1–3.—Patient was given 0.25 mg. (10,000 units) calciferol daily. Faecal calcium was equal to dietary intake with low normal urine calcium. The slightly lowered faecal calcium in period 3 is exactly accounted for by slightly lowered faecal nitrogen, and is therefore due to variation in faecal collections. The net balance for calcium was negative. Phosphorus and nitrogen balance was positive.

Six-day Periods 4, 5, and 6.—Patient was given calciferol 10 mg. (400,000 units) daily by mouth. This resulted in a steady decrease in faecal calcium with a slight rise in urine calcium, bringing the patient into strongly positive balance for calcium and phosphorus. The rapidity of this response shows that the dose of calciferol was unnecessarily high. With the improvement in the calcium and phosphorus balance the serum inorganic phosphorus rose from 2.6 mg. to 3.6 mg. per 100 ml.

Discussion

Osteomalacia results from under-saturation of body fluids with respect to calcium and phosphate ions. This leads to a failure to precipitate calcium salts in the organic matrix of bone. It is manifested by a lowered serum calcium or inorganic phosphorus, or both, with demineralization of bones. The latter may be generalized or localized in the pseudo-fractures described by Looser, and which Albright and Reifenstein (1948) considered to be pathognomonic of osteomalacia.

Osteomalacia can occur from a variety of conditions which, by one means or another, lower the ionic product of calcium × phosphorus. These are now considered in relation to our own patient.

1. Dietary.—Deficiency of calcium salts or vitamin D. Our patient's diet contained a high proportion of bread and cheese containing adequate calcium salts, and was in fact deficient only in ascorbic acid, and even this had caused no signs or symptoms of scurvy.

2. Absorption Defect.—The commonest cause of osteomalacia in this country is steatorrhoea. The patient gave no history of bowel abnormality. A 12-day fat balance showed 93% of fat absorption on a daily intake of 80 g., during which time metabolic studies showed him to be in negative calcium balance. Moreover, a normal urine calcium excretion virtually excluded a diagnosis of steatorrhoea.

3. Renal Acidosis.—The patient did not have acidosis. Urine calcium was not high. He did not have aminoaciduria.

4. Resistant Rickets Group—Renal Tubular Defect with Hypophosphataemia.—Balance studies show that on a normal intake of calcium and phosphorus, and despite 0.25 mg. (10,000 units) of calciferol daily, he still failed to maintain a normal serum inorganic phosphorus and was in negative balance for calcium, mainly due to high faecal excretion. The positive balance for phosphorus was accounted for by the positive nitrogen balance. On administration of 10 mg. (400,000 units) of calciferol daily, the patient went into strongly positive calcium and phosphorus balance, and the serum inorganic phosphorus rose from 2.4 to 3.7 mg. per 100 ml. He has since been maintained on half of this dosage of calciferol, with remission of all symptoms and healing of his pseudo-fractures.

This type of balance chart is highly characteristic of cases of resistant rickets in adults or older adolescents. The total lack of response to 10,000 units of calciferol daily is quite unlike other types of osteomalacia, which are

particularly sensitive to these small doses (Bauer and Marble, 1932). On the other hand, the immediate and considerable improvement in calcium and phosphorus balance on massive doses of calciferol indicates that osteomalacia is present but "resistant" to doses of calciferol which would cure other types of the disease than resistant rickets. It has been shown by Bauer, Marble, and Claflin (1932) that normal subjects on large doses of calciferol will show a prompt improvement in absorption of calcium and phosphorus, but, unlike osteomalacics, there is an equally great increase in urinary calcium and phosphorus, so that the calcium and phosphorus balance is not improved. In our case the marked improvement in calcium and phosphorus balance on high doses of calciferol confirms that the patient was suffering from osteomalacia.

The histological criterion of active osteomalacia is the presence of excessive osteoid disposed as wide bands of palely staining tissue on the surface of both compact and trabecular bone. In the present case, although evidence of osteomalacia had been clear, the absence of this histological feature at the time of biopsy after three months of high dosage with vitamin D indicates that remineralization of osteoid had been effected.

Summary

Metabolic balance studies on a case of von Recklinghausen's neurofibromatosis with osteomalacia is presented.

The association of the two diseases is noted, and proved cases previously mentioned in the literature are quoted.

The aetiology of the osteomalacia is shown to be a renal tubular defect, presumably congenital, which brings it into the group of diseases usually known as resistant rickets.

Bone biopsy showed that there is osteoporosis as well as osteomalacia. The cystic appearance of bone is due to combined osteoporosis with deep indentation of bone by mucoid fibrous tissue originating from the periosteum. There was no histological evidence of osteomalacia at the time of biopsy, presumably as a result of treatment.

We wish to thank Dr. James Dow for referring this case to us; Mr. John W. Woollen for the serum analyses and fat balances; Miss Patricia Carroll for her help in the routine chemical investigations; and the nursing staff of the metabolic unit for their care of the patient during the prolonged periods involved in these balances.

Chemical Methods

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POST-OPERATIVE STAPHYLOCOCCAL ENTEROCOLITIS DURING ANTIBIOTIC THERAPY

BY

B. J. FOWLER, F.R.C.S.

Lately Senior Surgical Registrar, Derby

Staphylococcal enteritis during antibiotic therapy is now of clinical importance. An antibiotic-induced intestinal bacterial vacuum in the recipient renders conditions very suitable for colonization by resistant staphylococci (Smith, 1952). Though chlortetracycline ("aureomycin") and oxytetracycline ("terramycin"), the most potent producers of an intestinal bacterial vacuum, have normally been incriminated, chloramphenicol, and penicillin and streptomycin together, have also been blamed. Zischka (1950), quoted by Herrell *et al.* (1953), even described a case following sulphaguanidine therapy. Parenteral administration has also produced the condition (Reiner *et al.*, 1952; Fairlie and Kendall, 1953; Herrell *et al.*, 1953). The normal post-operative increase in adrenocortical hormones may account for the infection gaining a hold, even in some cases without the aid of antibiotics (Herrell *et al.*, 1953). It seems justifiable to differentiate staphylococcal enteritis from post-operative pseudo-membranous enteritis; Prohaska *et al.* (1954), Dearing and Heilman (1953), and Pettet *et al.* (1954) are also of this opinion.

Cross-infection is the main factor in its causation. Cases have been described by Kramer (1948), Reiner *et al.* (1952), Dearing and Heilman (1953), Gardner (1953), Terplan *et al.* (1953), Wakefield and Sommers (1953), Hay and McKenzie (1954), Choremis *et al.* (1954), Williams (1954), Spink (1954), Bowie (1954), and Fairlie and Kendall (1953).

Three further cases are now recorded.

Case 1

A small, ill woman aged 68 had a strangulated femoral hernia repaired, 4 cm. of severely affected ileum being returned to the abdomen. She received 1 g. of streptomycin and 300,000 units of aqueous procaine penicillin intramuscularly twice daily for 4½ days. The streptomycin totalled 9 g. The wound suppurated and local infection increased over the next two days. The pus was not cultured. Her general condition deteriorated. Oral chloramphenicol, 0.5 g. six-hourly, was begun at 10 a.m. on the sixth day after operation. Two days later the wound was only slightly inflamed, and her general condition had so improved that provisional arrangements for her return home were made.

However, the next day she vomited several times and had severe diarrhoea. Her throat was red and sore. Chloramphenicol was stopped, a total of 6.5 g. having been given. She deteriorated with vomiting, diarrhoea, and circulatory collapse, and died ten days after operation.

At necropsy, otherwise healthy small and large intestines were full of a creamy and practically odourless light-yellow fluid. Acute infantile gastro-enteritis was simulated. This observation led to culture of the fluid, which gave a growth of coagulase-positive staphylococci insensitive to penicillin, sulphathiazole, streptomycin, chloramphenicol, and chlortetracycline. It was concluded that staphylococcal enteritis caused death.

Case 2

A man aged 35 with Crohn's disease received pre-operatively 26 g. of succinylsulphathiazole in 5½ days and streptomycin 2 g. and 1 g. on the two days before operation.