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Hypercalcaemia and hypokalaemia in tuberculosis

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Bradley, G W, and Sterling, G M (1978). *Thorax*, **33**, 464–467. **Hypercalcaemia and hypokalaemia in tuberculosis.** In two patients with extensive pulmonary tuberculosis who developed hypercalcaemia and hypokalaemia the hypercalcaemia appeared related to the use of small doses of vitamin D, which suggested patients with tuberculosis were hypersensitive to vitamin D. They were thus similar to patients with sarcoidosis, and it is interesting that the Kveim test result was positive in both cases. The hypercalcaemia was quickly suppressed with steroids. Hyperparathyroidism, thyrotoxicosis, Addison's disease, and multiple myeloma were excluded on clinical grounds and by the appropriate tests. The hypokalaemia was associated with increased renal excretion of potassium, and was probably due to distal tubular damage from hypercalcaemia.

Patients with tuberculosis tend to have a total plasma calcium concentration on the low side of normal (Kaminsky and Davidson, 1931), possibly due to abnormalities in plasma protein. In contrast with this, patients with sarcoidosis tend towards hypercalcaemia due to an increased sensitivity to vitamin D (Bell *et al*, 1964). An association between hypercalcaemia and tuberculosis has seldom been reported, but Shai *et al* (1972) described ten such patients. We describe two further patients in whom extensive tuberculosis was complicated by hypercalcaemia and other electrolyte disorders.

Case 1

A 26-year-old man was admitted to hospital in February 1977 with a short history of malaise, shortness of breath, productive cough, and leg swelling. He was a heavy drinker who had been admitted to hospital six months previously with acute pancreatitis; at that time his chest radiograph was normal. On examination he was ill and wasted with pitting oedema of the legs and clinical signs of a left pneumothorax. His chest radiograph confirmed the left pneumothorax and also showed tuberculosis in the right lung, confirmed by sputum culture. The oedema disappeared when his initial hypoalbuminaemia improved, and his sputum became free of acid bacilli on treatment with streptomycin, isoniazid, and ethambutol. He was also put on pyridoxine and multivite tablets. His general condition, however, failed to improve, and ten weeks after admission hypercalcaemia and hypokalaemia were discovered.

Case 2

A 31-year-old man, also a heavy drinker, was admitted to hospital in February 1974 with a six-week history of malaise, shortness of breath, night sweats, and productive cough. His chest radiograph showed widespread bilateral cavitating tuberculosis, and acid fast bacilli were found in (and subsequently cultured from) his sputum. He was treated with streptomycin, isoniazid, and PAS in conventional doses and also given pyridoxine and multivite tablets. Despite radiographic improvement and elimination of *Mycobacterium tuberculosis* from his sputum, his general condition failed to improve. Hypercalcaemia and hypokalaemia were found 18 weeks after admission.

Progress of metabolic disorders

The evolution of the electrolyte disorders is shown in fig 1 (case 1) and fig 2 (case 2). Both patients were hyponatraemic on admission, but this had either improved (case 1) or returned to normal (case 2) by the time the clinical condition began to deteriorate. In both cases hypokalaemia developed as hypercalcaemia became apparent. Despite hypokalaemia the 24-hour urine potassium excretion was not decreased—33 mmol/24 h in case 1 and 66 mmol/24 h in case 2 (before steroids

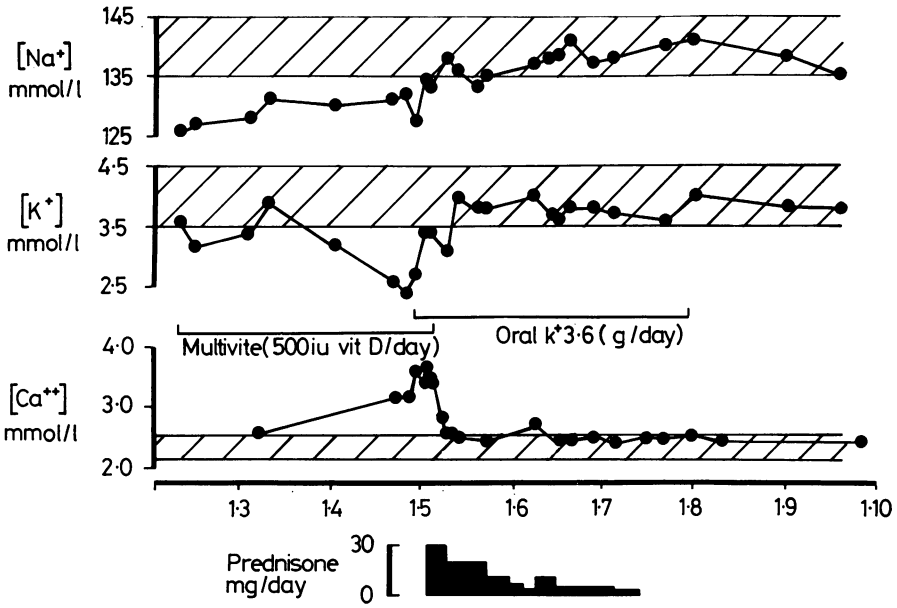

Fig 1 *Plasma sodium, potassium, and calcium concentrations for case 1; normal range shaded. Day and month is indicated on abscissa. Multivite tablets, oral potassium, and prednisone were given for time at dosage indicated.*

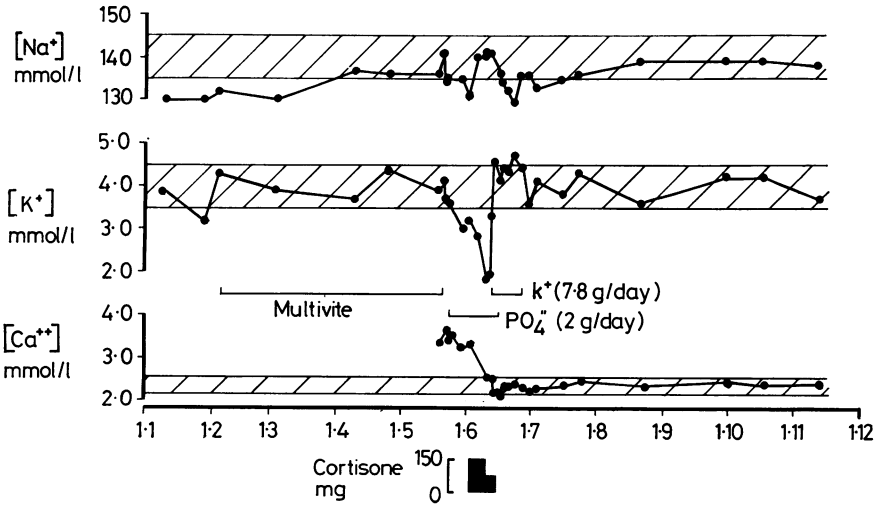

Fig 2 *Plasma sodium, potassium, and calcium concentrations for case 2; normal range and treatment indicated as in fig 1.*

and potassium supplements had been started). In case 2 the hypokalaemia became quite profound when steroids were given, but in both cases the hypokalaemia responded to potassium supplements. Multivite tablets (two tablets a day each containing 500 IU vitamin D) were stopped when the hypercalcaemia became apparent. Steroids quickly suppressed the hypercalcaemia and were eventually withdrawn without return of the metabolic disorders. After correction of the hypercalcaemia the subsequent recovery of the patients was uneventful.

The calcium values shown in figs 1 and 2 were measured from blood samples obtained without venostasis but were not corrected for abnormalities in plasma protein. The non-protein-bound calcium was calculated using the formula given by Moore (1970) and is shown, along with the plasma albumin and globulin, in figs 3 and 4. The high diffusible calcium was associated with a high urine excretion of calcium in both cases (10·5 mmol/24 h in case 1 and 13·9 mmol/24 h in case 2).

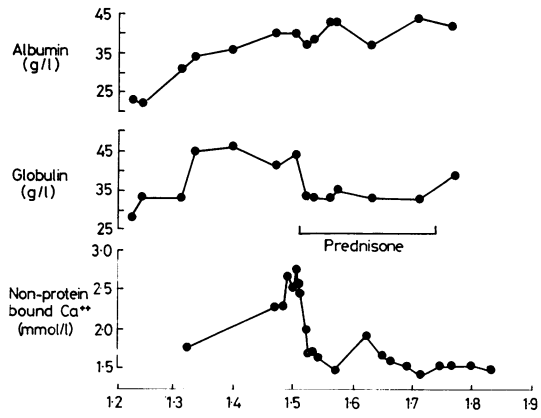

Fig. 3 *Plasma albumin, globulin, and non-protein-bound calcium for case 1. Date on abscissa.*

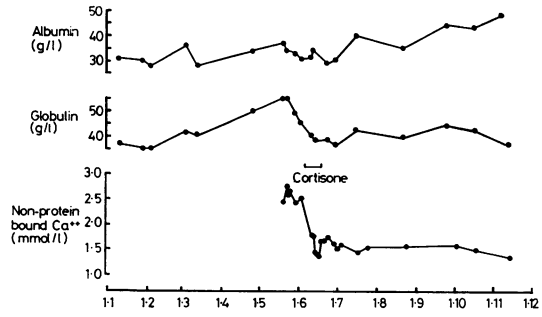

Fig 4 *Plasma albumin, globulin, and non-protein-bound calcium for case 2. Date on abscissa.*

Deterioration in both cases was associated with a rise in plasma globulin due to a diffuse increase in gammaglobulin. In case 1 this rapidly returned to normal on the introduction of steroids, but in case 2 the globulin concentration fell sharply before steroids were introduced. Both patients had initially low albumin concentrations which subsequently improved.

The Kveim test result was positive in both patients. The Mantoux test result was positive in case 1 after withdrawal of steroids and there was a grade 2 response to a Heaf test in case 2 at the beginning of the illness.

Discussion

Clinical deterioration in these patients with extensive pulmonary tuberculosis was associated with the development of hypercalcaemia and hypokalaemia. Changes in total plasma calcium concentrations could not be accounted for by a rise in plasma globulin because the non-protein-bound calcium was also raised. The increase in diffusible calcium was also reflected in a rise in calcium excretion. Hypercalcaemia can be associated with distal tubular damage producing increased potassium excretion (Ferris *et al,* 1961), and the hypokalaemia was probably due to this mechanism.

The cause of the hypercalcaemia in these two patients remains uncertain, but several possibilities were excluded. Failure to detect parathyroid hormone in the blood of case 1 and the demonstration of normal tubular phosphate reabsorption were against a diagnosis of hyperparathyroidism. Plasma phosphate and alkaline phosphate concentrations were normal in both cases. The rapid response to steroids and the subsequent course of the illness were unlike hyperparathyroidism.

Addison's disease may occur in tuberculosis and can be associated with hypercalcaemia. The diurnal cortisol levels measured in case 1 were high. In both cases the abdominal radiograph was normal, and steroids were withdrawn without clinical deterioration. There was, therefore, no evidence of Addison's disease. Thyrotoxicosis was excluded by thyroid function tests and multiple myeloma by plasma protein electrophoresis, since both these conditions can be associated with hypercalcaemia. There was no evidence of malignant disease.

Two points are of particular relevance to the development of hypercalcaemia in these patients. Both patients had positive Kveim test results, and both were on vitamin supplements containing small quantities of vitamin D. Patients with sarcoidosis are known to be sensitive to small doses

of vitamin D, which causes increased intestinal absorption of calcium (Bell *et al*, 1964). The reason for this increased sensitivity is unknown, but patients with tuberculosis may have a similar hypersensitivity to vitamin D. Of the ten patients with hypercalcaemia and tuberculosis described by Shai *et al* (1972), six were known to be on vitamin D supplements and two had positive Kveim test results.

Although Shai *et al* (1972) described ten cases showing an association between tuberculosis and hypercalcaemia, there are few other recent case reports describing such a link (Sharma *et al*, 1972; Braman *et al*, 1973). The relationship was recognised in the older literature, however, when hypercalcaemia was described in patients treated with cod liver oil (Kaminsky and Davidson, 1931). This experience suggests that vitamin D should be used in patients with tuberculosis only when there is a specific indication, and then only with great care.

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