MEDICAL PRACTICE

Clinical Endocrinology

Diagnosis and Treatment of Hypercalcaemia

LYAL WATSON

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A raised plasma calcium level is an important disorder in clinical medicine, for it occurs quite commonly in several diseases and may produce severe symptoms and definite pathological changes. Hypercalcaemia can be defined with precision and its cause can usually be established with certainty. In most cases it can be corrected by appropriate treatment with relief to the patient.

Aetiology and Pathogenesis

The plasma calcium level is normally maintained within a narrow range despite relatively large daily exchanges of calcium between the intestine, the bloodstream, the kidneys, and the bones. The parathyroid hormone and vitamin D provide the two main physiological regulating mechanisms; the role of calcitonin is still uncertain.

It is generally agreed that the principal function of parathyroid hormone is to maintain a normal plasma calcium level, and that the main role of vitamin D is to stimulate the gastrointestinal absorption of calcium. The precise way in which parathyroid hormone regulates the plasma calcium level is still being debated. The view most commonly held is that its prime action is to control the dynamic exchange of calcium between the bones and the blood stream.¹⁻³ Others consider that its control over renal excretion and perhaps gastrointestinal absorption of calcium are more important than any effect on bone in the physiological regulation of normal plasma calcium levels.⁴

There have been great advances during the last decade in our knowledge of the chemistry and metabolism of parathyroid hormone and vitamin D. Both bovine and porcine parathyroid hormone consist of 84 amino-acids and a synthetic fragment containing the first 34 amino-acids in sequence from the amino-terminal will produce the major effects of the hormone.⁴

Equally striking have been the discoveries that vitamin D is converted in the liver into an active metabolite—25 hydroxy-cholecalciferol—which is then converted in the kidney into another metabolite—1, 25 dihydroxycholecalciferol.⁵ These latter substances appear to be responsible for the actions of vitamin D at the cellular level.

CAUSES

The clinical causes of hypercalcaemia are classified in the Table. Primary and tertiary hyperparathyroidism⁶ are due to excessive secretion of parathyroid hormone from parathyroid

Causes of Hypercalcaemia

- (1) Excessive parathyroid secretion
 - (a) primary and tertiary hyperparathyroidism
- (2) Excessive administration of vitamin D, or calcium, or both
 - (a) self medication with vitamin preparations
 - (b) accidental overdosage in treatment of hypocalcaemia or other conditions
 - (c) milk-alkali syndrome
- (3) Increased sensitivity to small doses of vitamin D
 - (a) sarcoidosis
 - (b) perhaps some cases of "idiopathic" hypercalcaemia of infancy
- (4) Bone diseases
 - (a) secondary carcinoma involving bone
 - (b) multiple myeloma, leukaemia, Hodgkin's disease, and other reticuloses involving bone
 - (c) Paget's disease (in periods of increased activity or after immobilization rarely in osteoporosis due to
 - (d) (1) immobilization especially in childhood
 - (2) thyrotoxicosis
- (5) Other causes
 - (a) carcinoma, sarcoma, and reticuloses without bony involvement
 - (b) adrenal insufficiency
 - (1) acute following adrenalectomy
 - (2) Addison's disease (rarely)
 - (c) hypercalcaemic periostitis

tumours—usually a single adenoma, less commonly multiple adenomata or diffuse hyperplasia of all the parathyroid tissue, rarely a parathyroid carcinoma.

In the conditions grouped under headings (2) and (3) in the Table hypercalcaemia is associated with excessive absorption of calcium from the gut due to excessive administration of vitamin D or calcium or to increased sensitivity to physiological amounts of the vitamin. The latter has been well documented in sarcoidosis.⁷

In osteolytic bone disease hypercalcaemia may result from the liberation of calcium from the bones into the blood stream more quickly than the kidney can clear the blood of the excess calcium. This mechanism is seen most commonly in patients with bony metastases from tumours arising in several primary sites. Besides this local effect malignant tumours may produce humoral substances, modifying calcium metabolism and raising the plasma calcium without invading the bones. Several tumours have been shown to contain a substance with many properties of parathyroid hormone; other tumours may produce other chemicals which may raise the plasma calcium.⁸

Prevalence

Though malignant tumours of non-parathyroid origin cause hypercalcaemia in most cases, *prolonged sustained* hypercalcaemia is most commonly due to a parathyroid tumour. Probably the prevalence of parathyroid tumours is greater than 1 case per 1,000 of the population.⁹ They occur about three times as commonly in women as in men; they are rare before the age of 20, but then increase in prevalence decade by decade.

Common malignant tumours of non-parathyroid origin which regularly cause hypercalcaemia include carcinoma of the breast, bronchus, kidney, stomach, and uterus as well as the lymphomas. In these cases hypercalcaemia usually occurs at a relatively late stage of the illness when metastasis has occurred or the primary tumour has become apparent. Sometimes, however, it is the earliest manifestation and may cause problems in differential diagnosis.

The other conditions shown in the Table produce hypercalcaemia much less frequently than either parathyroid tumours or non-parathyroid cancers.

Clinical Features

Hypercalcaemia from any cause may give rise to widespread symptoms and any doctor should bear the possibility of the diagnosis in mind. Symptoms include generalized weakness, tiredness and lassitude, anorexia, nausea, and sometimes vomiting, constipation, thirst, dry mouth, nocturia, inability to concentrate, drowsiness, and more serious mental symptoms. Usually these symptoms are mild but sometimes severe nausea and vomiting, dehydration, obstinate constipation, or psychosis may produce serious problems.

RENAL DISORDERS

Renal tubular and glomerular function may become impaired and hypertension may follow in prolonged cases. Hypercalcuria, sometimes with renal stone formation or nephrocalcinosis, usually accompanies hypercalcaemia unless renal failure is severe. Renal stones are rare in hypercalcaemia due to non-parathyroid cancers, even when hypercalcuria is pronounced and prolonged—a point of differential diagnostic value and of theoretical interest.

CORNEAL CALCIFICATION

Corneal calcification is the most striking physical sign of hypercalcaemia and if sought regularly may lead to the discovery of otherwise inconspicuous hypercalcaemia. It consists of a thin linear aggregation of coarsely granular or gritty appearance which occurs in the cornea close to the corneoscleral junction on the medial and the lateral sides. It is best seen with a hand lens and a strong light shone in from the side. It was found in about a quarter of the first 300 patients with parathyroid tumours treated at University College Hospital.

Diagnosis

Whatever the clinical presentation, the final diagnosis of hypercalcaemia must be made in the laboratory. This requires the careful definition of normal ranges for the plasma calcium under standard conditions in individual laboratories.

Blood should be taken from patients in the fasting state to avoid postprandial fluctuations. Whether or not venous occlusion has been applied, allowance must be made for variation in plasma protein concentration since the protein-bound fraction accounts for up to 40% of the total plasma calcium. Changes in the plasma protein concentration are in general reflected by the plasma specific gravity and the plasma calcium rises or falls by about 0.25 mg/100 ml for each unit change in the third decimal place of the plasma specific gravity. The normal value is taken as 1027 and 0.25 mg/100 ml is added to or subtracted from the plasma calcium for each unit change down or up, respectively, from this baseline.¹⁰ The correction is inaccurate if the plasma protein level is very low, or if the distribution of protein fractions is abnormal.

The normal range in adults for fasting plasma calcium corrected for specific gravity is 8.9 to 10.2 mg/100 ml as determined in the metabolic laboratories at University College Hospital.¹¹ The Mayo Clinic team have reported an almost identical range of 8.9 to 10.1 mg/100 ml.¹² Marginal hypercalcaemia may be missed in laboratories where the normal range is wider than these. Direct determination of the physiologically important plasma-ionized calcium fraction gives further precision to the definition of these marginal cases.

Differential Diagnosis

CLINICAL AND RADIOLOGICAL ASSESSMENT

There is no substitute for careful clinical assessment in determining the cause of hypercalcaemia. A history of excessive ingestion of milk, alkalis, or preparations containing vitamin D, evidence of a primary or metastatic carcinoma, or physical signs of sarcoidosis must not be overlooked. Radiological assessment may also provide valuable signs of osteitis fibrosa or other bone disease, of sarcoidosis, primary or secondary carcinoma, or renal calcification.

LABORATORY PROCEDURES

Other procedures are of value in the differential diagnosis.

Phosphate Studies.—The fasting plasma phosphorus level is nearly always low (3 mg/100 ml or less) in adults with hyperparathyroidism and normal renal function; it is usually normal in hypercalcaemia due to other causes. Nevertheless, a low plasma phosphorus level is of limited differential value in individual cases because it is sometimes found in hypercalcaemia of any cause.¹³ More complicated tests of phosphate excretion provide little further help.

Multivariate Analysis.—The results from estimating the levels of plasma chloride, bicarbonate, urea, and alkaline phosphatase may be helpful, especially in conjunction with the plasma phosphorus levels. Analysis of the results of these five determinations obtained from hypercalcaemic patients immediately after admission to hospital led to diagnoses which coincided with the final diagnosis in over 90% of cases.^{14*} The two discriminant functions involved in the analysis can be calculated from equations or determined accurately from nomograms so that this technique is available quickly and easily in any centre.

Hydrocortisone Test.—In patients with parathyroid tumours without osteitis fibrosa the plasma calcium level does not usually fall in response to the administration of hydrocortisone, 40 mg every 8 hours for 10 days. In most other hypercalcaemic conditions there is a significant fall in the plasma calcium level in response to the test.¹⁰ The use of prednisone or other related steroids is not recommended since the equivalent doses have not been established for this test.

*In this article the formula for the second discriminant function was printed incorrectly. It should read as follows:
Second discriminant function
= (0.0038 × inorganic phosphate in mg/100 ml) +
(4.193 + log alkaline phosphatase in K.A. units/100 ml) +
(0.0648 × chloride in meq/l) — (0.1085 × bicarbonate in meq/l) +
(1.384 × log urea in mg/100 ml).

Parathyroid Hormone Assay.—The sensitivity of this assay system varies greatly from laboratory to laboratory. One group of workers have described an assay of great sensitivity and discrimination, demonstrating raised levels of parathyroid hormone in the circulation in all cases of hyperparathyroidism.¹⁵ All other workers have achieved less sensitivity and still find overlap between cases of hyperparathyroidism and the normal range.^{4 12 16 17} Selective venous catheterization has been used as an additional diagnostic aid in these circumstances and also for the pre-operative localization of parathyroid tumours.⁴

DOUBLE DIAGNOSIS

Parathyroid tumours sometimes occur in patients with other causes of hypercalcaemia—including non-parathyroid cancers, sarcoidosis, thyrotoxicosis, and Paget's disease. Differential diagnosis is more complex in these cases but the various procedures described above will usually lead to accurate diagnosis of each condition.

Treatment

Hypercalcaemia can usually be corrected and its symptoms relieved, in many cases by removing the cause. In emergencies phosphate loading will lower the plasma calcium whatever the cause.¹⁸ This may be given intravenously as the neutral sodium salt, using doses of one or two grammes of phosphorus in the first 24 hours. Later, phosphate can usually be given orally as disodium hydrogen phosphate, 10 grammes daily (containing about 2 g of phosphorus).

In hyperparathyroidism parathyroidectomy is a standard procedure which we recommend in all patients with symptoms. The Mayo Clinic team on the other hand, have suggested more restricted indications for surgery.¹² Postoperative medical management usually presents problems only in cases with osteitis fibrosa, when treatment with vitamin D, calcium supplements, and aluminium hydroxide gel may be necessary for some weeks or months.

In the conditions grouped under headings (2) and (3) in the Table the treatment is to stop the excess intake of calcium or vitamin D. Hydrocortisone may be a valuable short-term addition to this treatment.

In the hypercalcaemia of cancer, treatment is more palliative, though removal of an operable tumour may be effective in some cases.¹⁹ Local radiotherapy may produce temporary improvement as may antimitotic agents, especially in multiple myeloma and the lymphomas. Hypercalcaemia usually returns

when the tumour grows again or when secondary deposits appear.

The administration of corticosteroids produces a good result in some patients with cancer.²⁰ In others who show only a partial response to corticosteroid administration, satisfactory results can be obtained by adding oral sodium or potassium phosphate. Oestrogens and androgens have been used successfully in the palliative treatment of hypercalcaemic patients with breast cancer and bony metastases.

Disodium ethylenediamine tetraacetic acid given intravenously will lower the plasma calcium level, but its effect is transient and in large doses renal damage may occur. It has contributed little to the management of hypercalcaemia in cancer. The role of other agents which produce hypocalcaemia (calcitonin, glucagon, diphosphonates) is being investigated.

Finally, it should be noted that the early occurrence of hypercalcaemia in patients with cancer does not necessarily mean a bad immediate prognosis. Some patients survive for years after treatment of severe hypercalcaemia, which is actually the cause of all their initial symptoms.

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Scientific Basis of Clinical Practice

Disordered Leucocyte Proliferation in Leukaemia

JOHN STUART

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The application of leucocyte isotope-labelling techniques to the study of acute and chronic leukaemia has provided considerable insight into the disordered leucocyte proliferation which

characterizes these diseases. In acute leukaemia a maturation arrest in the leukaemic cell line occurs at the blast-cell stage of development and results in a failure to produce the normal, functional end-cells of that cell line. Extensive replacement with blast cells then leads to a failure to produce the functional units of the other marrow cell lines; this results in the early development of neutropenia, thrombocytopenia, and anaemia, which characterize acute leukaemia. In chronic leukaemia there is

The Children's Hospital, Ladywood, Birmingham
JOHN STUART, M.D., M.R.C.P., Consultant Haematologist