Clinicopathological Conference

A case of diabetes

DEMONSTRATED AT THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

The sixteenth quarterly clinicopathological conference was held at the Royal College of Physicians of London on 28 July. Professor R Mahler (1) took the chair and Dr T M Hayes (2) presented the case.

Clinical summary

The patient, a young woman born in West Wales in 1951, was delivered normally at full term and an only child. There was no relevant family history. She had an uneventful childhood until she was 8. Then she had a short period of polyuria and thirst and was found to have diabetes mellitus. The rest of her childhood was tempestuous. She was admitted to hospital many times with hyperglycaemia and hypoglycaemia until she was 15. Her growth was satisfactory. She was treated at first with lente insulin and later with twice daily soluble insulin and insulin zinc suspension (Insulin Semilente). In her teens she was put on a mixture of soluble and isophane insulin in the morning and soluble insulin at night. She reached menarche at 14, but her periods were always irregular. Despite many hospital admissions she studied pharmacy at university.

In 1972, aged 21, she qualified as a pharmacist. In 1973 she transferred to our diabetic clinic. She weighed 69·6 kg, 26", more than her ideal weight of 55 kg. Her diabetic control was only fair. She often had high blood sugar concentration and also hypoglycaemic reactions. She had scattered microaneurysms—her only serious diabetic complications—but no other evidence of retinopathy. She had areas of fat atrophy and hypertrophy at the insulin injection sites. We reduced her diet to 5 MJ (1200 kcal) a day, including 120 g of carbohydrate. Her insulin was changed to a mixture of neutral and isophane twice a day.

In 1975 she still weighed 10 kg above her ideal weight, and diabetic control was still unsatisfactory, though she did not have to be admitted to hospital. She still had fat atrophy and local reactions at the injection sites, itchy lumps lasting for 24–48 hours. Her insulin was changed to a monocomponent type (Semitard), twice a day, and there were no more local reactions.

In June 1976 she went on holiday to Ireland. On her way home by sea she become ill with nausea and vomiting, which she attributed to seasickness. But it lasted a long time, and she was admitted to a hospital near her home. The nausea and vomiting were very troublesome, particularly in the early morning, and her diabetes was hard to control. She also complained of giddiness, but it was not known how far this was due to hypoglycaemia. She became malnourished, and her diabetes called for treatment with frequent intravenous fluids. Her plasma sodium and chloride concentrations were low normal.

After six weeks in hospital she was transferred to the University Hospital of Wales. She was drowsy and dehydrated and had signs of recent loss of weight. She had a sinus tachycardia (100/minute) but no fever. Her blood pressure was 110/60 mm Hg. There were no focal neurological signs. The few microaneurysms in her retinas were unchanged. Biochemical investigations showed the following concentrations: plasma sodium 133 mmol (mEq)/l, plasma potassium 3·1 mmol (mEq)/l, blood urea 4·0 mmol (24·1 mg/100 ml), plasma calcium 3·04 mmol (12·2 mg/100 ml), plasma phosphate 0·89 mmol (2·7 mg/100 ml), and plasma albumin 28 g/l. The haemoglobin was 7·6 g/dl with a normochromic and normocytic film. The electrocardiogram then, and over the next few weeks, showed various abnormalities in the T waves, which were thought to be non-specific.

She was treated with a continuous infusion of neutral insulin (Actrapid), rehydrated with intravenous fluids, given intravenous nutrition (amino-acids and fat emulsion), and we ensured that she did not develop hyperchylomicronaemia by monitoring the appearance of her plasma. Over the next few days her plasma sodium concentration varied from 123 to 133 mmol (mEq)/l, and her urea from 1·8 to 4·0 mmol/l (10·8 to 24·1 mg/100 ml). Her plasma calcium concentration fell to 2·44 mmol/l (9·75 mg/100 ml), and her phosphate concentration remained unchanged at 0·88 mmol/l.

Two days later she had a severe right upper lobe pneumonia, with high titres of antibody to Mycoplasma pneumoniae. Her diabetes was difficult to control, and she was often confused and disorientated. One night she collapsed and was hypotensive. The house physician on call from another firm rather empirically gave her dexamethasone, and she recovered rapidly.

Two-and-a-half weeks later she was well enough to get out of bed, but she became unconscious when she stood up—her blood pressure was 120/80 mm Hg lying down, but 50/30 mm Hg sitting and unrecordable standing.

During the first 16 days in hospital several changes took place in her calcium, phosphate, and albumin concentrations (see figure). Hypercalcaemia persisted for five days and reappeared about a fortnight later. A parathyroid hormone concentration of 0·3 ng/ml (upper limit of
normal — 1.0 ng/ml) corresponded at one stage with a serum calcium concentration of 2.53 mmol/l (10.1 mg/100 ml); when corrected for her hypoalbuminaemia her serum calcium concentration was 2.83 mmol/l (11.5 mg/100 ml).

Her urinary calcium excretion was slightly below the normal range and came just into the normal range after treatment. A straight radio- graph of the abdomen and radiographs of the hands showed no abnormalities. The thyroid profile showed a normal plasma thyroxine and normal free thyroxine index, but the thyroid-stimulating hormone was undetectable (less than 2.5 mU/l).
HYPERCALCAEMIA

DR PYKE: I am not quite so sure why she has hypercalcaemia. Two possibilities occurred to me. It might be the hypercalcaemia that is itself associated with Addison's disease, which is uncommon. On the other hand, as she is a pharmacist, she might have been taking calcium or vitamin D, although I think that vitamin D is excluded by the normal calciferol concentration. In view of what you said about her sensible personality I plump for the first explanation.

DR HAYES: Dr Pyke has, of course, got the story completely correct. By the time she was severely ill she had intermittent hypoponataemia, and hypotension developed during her pneumonia. The visiting house physician who gave her dexamethasone rather blindly made her very much better. She had hypercalcaemia. She had "normal" urinary 17-hydroxycorticosteroid and plasma cortisol concentrations at a time when she was under severe stress. So that led us on to adrenal stimulation tests. After 50 units of intravenous corticotrophin over four hours (see figure) her plasma cortisol concentration did not rise at all, although her basal levels were normal and her urinary 17-hydroxy-corticosteroid concentration did not rise after longer stimulation. So we had Addison's disease in what is called these days type 1B diabetes. Finally, her plasma parathyroid hormone (PTH) concentrations, which were inappropriately high, and which confused rather than helped us as we had no knowledge of plasma PTH concentrations in the hypercalcaemia of Addison's disease, returned to normal with treatment of her Addison's disease, as did the high calcium concentrations.

**Comments**

PROFESSOR MAHLER: Dr Pyke is to be congratulated on reaching a diagnosis in considerably less time than it took us. Any comments?

SIR DOUGLAS BLACK (4): What about pigmentation?

DR HAYES: The skin was entirely normal. There was no pigmentation or vitiligo.

DR P C FARRANT (5): I am interested in the anaemia. Did it get better? It can't have been due to haemolysis in the mycoplasma infection, can it?

DR HAYES: It was thoroughly investigated by our haematologist, who came to the conclusion that it was non-specific noriochrome normocytic anaemia associated with severe ill health. She had two marrow examinations. It was all corrected by the treatment for her Addison's disease.

DR PYKE: Of interest, but no importance—what is her tissue type? Is she HLA-B6?

DR HAYES: It should be but I don't know.

PROFESSOR R HOFFENBERG (6): I am sure Dr Pyke is correct in his diagnosis. Listening to his cross-examination of Dr Hayes, I wondered what he would have been like had he chosen law instead of medicine. I wonder if you are happy that you have excluded hyperparathyroidism. The cause of the hypercalcaemia in Addison's disease is obscure, and I was struck that the serum PTH concentration was measurable when it should not have been. I know that it should not have come down in response to dexamethasone but it does occasionally. Also one must try to relate the changes in serum calcium concentration to the concentration of serum albumin. Here the albumin concentration was low most of the time so that makes the high serum calcium concentration even more significant. Even towards the end her serum calcium concentration was still raised; did it come down to normal finally?

DR HAYES: The calcium concentration has been measured many times since her recovery and has always been normal; and her serum PTH concentrations have been appropriate, with normal albumin concentrations as well.

HYPERCALCAEMIA AND ADDISON'S DISEASE

PROFESSOR MAHLER: Dr Hayes, would you comment on the association between hypercalcaemia and Addison's disease?

DR HAYES: It was recognised in 1932, but was rediscovered in 1963, when there had been 16 cases reported. It is often seen after bilateral adrenalectomy for Cushing's syndrome. Five mechanisms have been suggested. The increased calcium absorption after removal of the normal inhibition of calcium absorption by steroids is one. This is refuted by the fact that if one puts dogs with hypercalcaemia due to adrenal insufficiency on a calcium-free diet they still maintain hypercalcaemia. Our patient was on a virtually calcium-free diet when she came to us. Secondly, haemoconcentration leading to raising of the plasma protein and calcium concentrations with increased affinity of protein for calcium has been suggested. Our patient was not haemoconcentrated, and her protein concentrations were low.

Thirdly, reduced renal excretion of calcium has been put forward. Our patient did have a reduced calcium excretion. Fourthly, it has been suggested that it is due to a thyroid-hormone-dependent increase in bone resorption after removal of inhibition by corticosteroids. In animals this hypercalcaemia disappears if the thyroid gland is removed.

The more recent suggestion, from Australia, was that it could be produced by an excessive production of 1,25-dihydrocalciferol. But the patient should have a high concentration and it was normal in our patient, although we tested it for the reason Dr Pyke suggested. There seems to be no information about serum PTH concentrations in patients with hypercalcaemia due to Addison's disease. One report does mention a patient who had typical hyperparathyroid changes in the hands, but no PTH concentrations were mentioned.

PROFESSOR MAHLER: So the only evidence for any of those mechanisms is the decreased calcium excretion?
Clinical Topics

Overdose from Lomotil

DIANNE PENFOLD, GLYN N VOLANS

British Medical Journal, 1977, 2, 1401-1402

Despite numerous reports on the hazards of taking overdoses of the anti-diarrhoeal agent Lomotil (atropine sulphate and diphenoxylate hydrochloride),1-3 these incidents still occur, sometimes being fatal. A prospective study was carried out by the National Poisons Information Service in 1976 to assess the extent of overdose with Lomotil.

Methods

For each call made to us from January 1 to 31 December 1976 asking for advice on treating a case of Lomotil overdose we sought further information on suspected dose, symptoms, treatment, and eventual outcome. From this information we tried to assess the relation between age and the severity of symptoms and between dose and severity. We classified each case according to the symptoms present on admission. Group 1 included people who showed no symptoms. Group 2 comprised those with pronounced symptoms: drowsiness, flushing, dry mouth, tachycardia, dilated pupils, rash, and nausea. Group 3 comprised patients with severe symptoms: grade IV coma, respiratory depression or arrest, or cardiac arrest.

Results and comment

Throughout the year 86 episodes of Lomotil overdose were reported, 71 of them in children aged under 5 (table I). Thirty-four of the patients had pronounced symptoms (group 2), and seven—all children under 12—were severely ill (group 3).

Further information was available for 48 cases (table II). Of the seven patients with group 3 symptoms, three had taken over 10 tablets of Lomotil, and the dose was unknown in the other four. Three of the 19 patients with pronounced symptoms had taken one to five tablets, three had taken six to 10, six had taken 11 to 20, two had taken 21-30, and five had taken an unknown number.

A 21-year-old who had ingested about 20 tablets suffered respiratory and cardiac arrest and died despite the administration of naloxone. On the other hand, a 2-year-old who was reported to have taken 20 tablets remained asymptomatic. Possibly the reported size of alleged doses was inaccurate, or young children may vary considerably in their response to an overdose of Lomotil. We reviewed data from earlier years to see whether they threw any light on the relation between dosage and the severity of symptoms. A 2-year-old boy reported to have ingested 12 tablets showed severe symptoms (cardiac arrest at eight hours) and died after three days with pneumonia and cerebral oedema (nalorphine was administered). Another 2-year-old presented in grade IV coma after a reported ingestion of only three or four tablets. He was given naloxone and finally regained consciousness two days after ingestion, and recovered fully after three days.

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