cells. We suggest that the term tertiary hyperparathyroidism should be restricted to those cases where a histologically proved adenoma is found.

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(Accepted 16 March 1978)

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Vitamin D transport in an infant with vitamin D toxicity

Massive doses of vitamin D lead to hypercalcaemia, but the mechanism is not fully understood. We studied the plasma binding of vitamin D and its major metabolite, 25-hydroxyvitamin D (25-OHD), in an infant with vitamin D toxicity.

Case report, methods, and results

A 9-month-old boy, born after a normal pregnancy, had been treated with vitamin D₂ drops (totalling 1 600 000 IU) from the age of 6 months because of delayed motor development. Two weeks before admission he developed polyuria and polydipsia. He was malnourished and had mild hypotonicity and muscle wasting. Blood urea nitrogen was 7.9 mmol/l (22 mg/100 ml); serum creatinine 14.1 µmol/l (0.16 mg/100 ml), calcium 2.88 mmol/l (11.5 mg/100 ml), phosphate 2.03 mmol/l (6.3 mg/100 ml); parathyroid hormone 350 ng/l (normal). Small radio-opaque stones were present in both kidneys. On a calcium-depleted diet, aluminium hydroxide gel, and phenobarbitone he showed improvement both clinically and biochemically (table).

Duplicate plasma samples were incubated with ³H-25-OHD and ¹⁴C-vitamin D at 4°C for 16 hours. The lipoproteins were separated by ultracentrifugation at a density of 1.21 g/ml. The lipoprotein-free plasma (density >1.21 g/ml) was electrophoresed on agarose gel and the protein bands were identified and radioassayed. In all the studies, 25-OHD was recovered in the α-globulin band where the specific vitamin-D-binding globulin appears on the chromatograph.¹ In contrast, the distribution of vitamin D was definitely affected by the hypervitaminosis (table). When the child was clinically toxic, 64% of the vitamin was found in the lipoprotein fraction, 15% in albumin, and only 21% in the α-globulin region. With clinical improvement, binding of vitamin D to plasma proteins gradually reverted to normal (table).

Comment

The physiological action of vitamin D is normally mediated through its active renal metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D),

whereas vitamin D itself lacks biological activity.¹ Synthesis of 1,25(OH)₂D is regulated, and is under negative feedback by high concentrations of calcium, phosphate, and 1,25(OH)₂D itself,¹ and moreover is normal in patients with hypervitaminosis D.² The concentrations of 25-OHD in patients with hypervitaminosis D (120 ng/ml in our case) are unlikely to cause clinical vitamin D toxicity since much higher concentrations occur in treatment with long-term vitamin D or 25-OHD without signs of toxicity.³ The cause should therefore be sought in vitamin D itself.

One explanation of the difference between the lack of physiological activity of vitamin D and its potential activity in hypervitaminosis may be an alteration in its normal binding to plasma proteins, as was found for the toxicity caused by vitamin A, another lipid-soluble vitamin.⁴ Under physiological conditions most vitamin D is transported on a specific binding globulin,¹ while the rest (up to 30-40%) is transported on plasma lipoproteins. The abnormal binding to lipoproteins and albumin in hypervitaminosis (table) may result in an uncontrolled transfer of the vitamin D molecule to cell membranes. The presence of large amounts of the parent vitamin D in a target organ such as the intestine might directly enhance calcium absorption, as shown when vitamin D was placed directly into tied duodenal loops in rats.⁵ This hypothesis is analogous to vitamin A toxicity, in which vitamin A is also displaced to lipoproteins from the vitamin-A-binding globulin.⁴

Supported by grants from the Ministry of Health and Joint Research Fund of the Hebrew University and Hadassah.

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(Accepted 15 March 1978)

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Hypokalaemic paralysis

The clinical effects of potassium depletion are variable. A patient presented with an illness clinically resembling acute postinfectious polyneuritis (Guillain-Barré syndrome).

Case report

A 60-year-old Australian became constipated during his journey to Britain, and on arrival vomited for a day. The next day he had pain in his calves and thighs, and subsequently developed progressive weakness of the legs and then of the arms, which advanced centripetally. One week later he had another short episode of vomiting, the paralysis increased so that he was bedridden, and a third episode of transient gastrointestinal disturbance occurred.

He had been hypertensive for several years, taking debrisoquine, chlor-

Serum concentrations of calcium, phosphorus, and 25-OHD, and binding of vitamin D and 25-OHD in plasma proteins (%)

Months after admission	Serum			¹⁴ C-vitamin D			³ H-25-OHD		
	Calcium (mmol/l)	Phosphorus (mmol/l)	25-OHD (ng/ml)	Lipoprotein	α-globulin	Albumin	Lipoprotein	α-globulin	Albumin
1	2.88	2.03	130	64	21	15	2	98	—
2	2.53	1.81	30	40	60	—	2	98	—
5*	2.8	1.94	—	48	52	—	2	98	—
6	2.38	1.68	30	30	70	—	2	98	—
Normal (mean ± SE)	2.13-2.5 (range)	1.29-1.78 (range)	<30	38 ± 2	62 ± 2	—	2	98	—

*After accidental feeding of vitamin-D-fortified milk.

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml. Phosphorus: 1 mmol/l ≈ 3.1 mg/100 ml.

thalidone, a low-salt diet, and a salt substitute containing 46% potassium as a food additive which he discontinued on leaving Australia. He was also taking a hay-fever remedy which contained liquorice. He was not generally dehydrated but had a dry mouth. Blood pressure was 160/100 mm Hg and the cardiovascular system was otherwise normal. The muscles were normal in appearance and consistency but he had tenderness of the thigh muscles and global weakness of trunk and limbs which was greater distally than proximally and greater in the legs than in the arms. He was unable to sit unaided or to walk. Extremes of gaze produced diplopia, and muscles of mastication were weak. Cranial nerve function was otherwise normal. Reflexes were depressed, ankle reflexes were absent, and plantars were flexor. There were no clear objective sensory findings although there was some patchy subjective sensory impairment.

Investigations showed a plasma potassium concentration of 1.8 mmol/l (1.8 mEq/l) with a 24-hour urinary excretion of 24 mmol potassium. Electrocardiogram (ECG) showed widened QRS complexes, slightly depressed ST segments in some leads, and asymmetrical T waves fused with U waves. The record was "compatible with" rather than "typical of" hypokalaemia.¹ The serum creatinine phosphokinase concentration (SCPK) was 3050 IU/l (normal 0-130 IU/l). Clinical response to oral potassium supplements was dramatic and within four days recovery was complete. The plasma potassium concentration was 3.5 mmol/l and the ECG normal. Five days later SCPK was 68 IU/l. Oral potassium was discontinued, the plasma potassium concentration fell, and the ECG abnormalities recurred. Fifteen months later he remained asymptomatic on debrisoquine, chlorthalidone, and potassium supplements, but the plasma potassium concentration was 2.7 mmol/l and 24-hour urinary excretion was raised at 119 mmol. No other defect of renal function was found, nor was primary hyperaldosteronism after adrenal function studies.

Comment

The ingestion of chlorthalidone and perhaps of liquorice and a defect of renal conservation of potassium contributed to the hypokalaemia in this patient. The clinical illness was precipitated by discontinuing a potassium-containing salt substitute. The raised SCPK concentration suggested a myopathy. A history of gastrointestinal disturbance followed by a progressive ascending, centripetal paralysis affecting bulbar musculature, associated with muscle pains and minimal sensory impairment, is highly compatible with a diagnosis of the Guillain-Barré syndrome,² although other possibilities such as polymyositis might be considered. Constipation was a clue to the hypokalaemia in this patient, but sphincter disturbances also occur in the Guillain-Barré syndrome.² In contrast to the dramatic clinical picture the ECG findings were unhelpful. In the investigation of paralysis it is essential to estimate the plasma electrolyte concentrations early.

I thank Dr P D Robertson for permission to report on his patient and for his advice; also Dr A F Lever and Dr A Calvert, who kindly supplied information, including the results of adrenal investigations.

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(Accepted 15 March 1978)

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Respiratory allergy to a factory humidifier contaminant presenting as pyrexia of undetermined origin

We report a patient who had attacks of fever which were particularly acute upon return to work after a weekend or other absence, but which improved during the working week. They were probably attributable to a reaction to contaminants growing in the factory humidifier system.

Case report

A 41-year-old man employed for four years in a printing factory had for 2½ years suffered from recurrent attacks of fever with malaise, headaches,

Reactions to inhalation tests with Coca's fluid and humidifier slime extract.

and breathlessness, which always started in the afternoon and persisted for up to 72 hours. At first they occurred about once a month, but more recently they had increased to three to four times a month. The results of extensive investigations were normal. After the fourth hospital admission his symptoms recurred whenever he returned to work, particularly after a prolonged absence, but improved during the working week. His symptoms were associated with a rise in temperature and fall in vital capacity. He was referred to the Brompton Hospital. He had no finger clubbing, and no wheezes or crackles in his chest. Results of chest radiography and lung function tests were normal. Two out of 32 other factory employees who were exposed to the same conditions had had similar but less severe symptoms.

The high quality printing work done at the factory required a constant level of humidity, which was achieved by passing air through water sprays in a chamber and then through ducts to the whole factory. The chamber had an unpleasant-smelling dark green slime on the walls below the water level, from which *Phialophora* sp, *Fusarium* sp, and *Cephalosporium* sp were isolated on culture. Freeze-dried extracts were prepared from the slime. Agar-gel double-diffusion tests gave positive precipitin reactions to an extract of the slime with the sera of the patient and four of the other 32 employees, including the two with symptoms. The patient's serum and two of these four positive sera also gave a positive reaction to *Phialophora* sp. Sera from 100 exposed control subjects gave no reaction.

Skin prick tests on the patient with common inhalant allergens and with freeze-dried humidifier slime extract in Coca's fluid plus 50% glycerol at concentrations of 0.1, 1, and 10 mg/ml elicited no reactions. The control inhalation test with Coca's fluid gave no reaction. Solutions of the freeze-dried extract of humidifier slime in Coca's fluid were tested at 0.1, 1, and 10 mg/ml on separate days. The concentration of 10 mg/ml provoked a parallel fall in FEV₁ (forced expiratory volume in 1s) and FVC (forced vital capacity), with a drop in the CO gas transfer factor (D_Lco) and in the CO gas transfer factor per unit alveolar volume (Kco) associated with a rise in temperature and recurrence of his symptoms (figure). No wheezing or prolongation of forced expiratory time was observed during the reaction.

Comment

The results of the inhalation test, supported by the occupational history and the precipitins, show that the patient was reacting to contaminants in the factory humidifier water. Of 32 comparably exposed workers, only four had precipitins, of whom two also had symptoms similar to those of the patient, suggesting a hypersensitivity reaction. The functional changes provoked by the inhalation test, with parallel falls in FEV₁ and FVC and an associated fall in Kco, suggest that this reaction occurred predominantly in the peripheral lung tissue, although the site of reaction can be identified with certainty only by histological evidence.

This pattern of reaction to the inhalation test is similar in nature, speed of onset, and duration to the "late alveolar reaction" elicited by appropriate antigens in extrinsic allergic alveolitis,¹ but this patient's illness differs from typical allergic alveolitis in several important respects. Whereas in allergic alveolitis continued antigenic exposure is associated with progressive symptomatic, functional, and radio-