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IDIOPATHIC HYPERCALCAEMIA OF CHRONIC DIALYSIS

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Summary

Three women on different forms of maintenance dialysis developed persistent steroid-responsive idiopathic hypercalcaemia, with low calcium absorption, severe skeletal decalcification, multiple fractures, and severe clinical problems. Bone histology showed osteomalacia with suppression of osteoblast activity and no hyperparathyroidism. The disease persists at least six months after transplantation. The features are compatible with poisoning by a toxin with many similar properties to aluminium: we only found significant aluminium overload in one of these cases.

Introduction

In 1980 Johnson [1] described three patients who, shortly after starting maintenance haemodialysis, developed severe persistent hypercalcaemia of unknown cause which was not reversed by parathyroidectomy. In one patient hypercalcaemia improved during two brief periods of renal transplantation, although we believe this improvement may have been due to the steroids given at the time. This paper describes detailed studies of three similar cases.

Case studies

Three post-menopausal women developed hypercalcaemia on maintenance dialysis. Hyperparathyroidism was excluded and there was no evidence of myelomatosis, sarcoidosis, neoplasia, or ingestion of vitamin D derivatives, calcium or alkali. Radiological skeletal surveys showed decalcification only. Isotope bone scans and thyroid function tests were normal. Hypercalcaemia was suppressed in all three cases by oral prednisolone, 30mg daily. Serum calcitonin concentrations, measured by an immuno-nuclear radioimmunoassay kit after adsorption on a sepharose column coated with rabbit anti-calcitonin, were elevated in two patients and normal in one (67% of our patients on dialysis are normal). Other investigations are summarised in Table I.

TABLE I

	Case 1	Case 2	Case 3
Age	52	50	42
Dialysis	Intermittent peritoneal	CAPD	Haemodialysis
Duration before hypercalcaemia	7 months	20 months*	17 months
Dialysate calcium mmol/L	1.80	1.75	1.55
Total serum calcium (mmol/L, normal 2.2–2.62)			
a) before dialysis	2.2	2.14	2.2**
b) at 'peak'	3.4	3.27	3.50
Serum ionised calcium (mmol/L, normal 1.05–1.27)	1.58	1.59	1.68
Serum alkaline phosphatase (iu/L, normal <85)	62 (later rose to 272)	60	130
Serum phosphate (mmol/L, normal 0.8–1.45)	2.34	1.2–2.2	1.24
Serum magnesium (mmol/L, normal 0.7–1.0)	1.3	1.27	1.23
Serum calcitonin after adsorption (normal <100pg/ml) (Immuno-nuclear radio-immunoassay)	141	37	196
Serum aluminium (μg/L)	250,150,70***	10****	132
Calcium absorption (single dose Ca^{47} % dose per litre plasma in 1 hour, normal >0.5%)	0.15%	0.05%	0.04%
Serum parathyroid hormone ('C' terminal assay, normal <1.3μg/L, in renal failure 90% >2.5)	0.8,1.2,2.6	1.8,0.69,0.17	Undetectable

* transient hypercalcaemia at 4–6 months
** after parathyroidectomy
*** May, June, July 1982
**** 3 months post-transplant

Case 1

A woman of 51 with cystinuria and pyelonephritis started maintenance intermittent peritoneal dialysis. Hypercalcaemia occurred after seven months and has persisted four years despite brief periods of haemodialysis and chronic ambulatory peritoneal dialysis. The patient had an acute neurological hypercalcaemic crisis. Serum alkaline phosphatase was initially normal but later rose to

200iu/L (normal < 85). Serum parathyroid hormone concentration checked in three separate laboratories using a different 'C' terminal radioimmunoassay was normal. Bone biopsy showed no osteitis fibrosa. There was severe osteopenia and the trabeculae comprised irregularly resorbed mineralised bone covered by excess lamellar osteoid including wide seams with five to seven lamellae lacking a mineralisation front on toluidine blue stain. Most seams appeared 'inactive'. A few seams showed a positive aluminon stain (aurine tricarboxylic acid) for aluminium deep to the osteoid. The overall appearance is similar to that of dialysis osteomalacia induced by aluminium.

Porcine calcitonin, as is often the case in renal failure [2], failed to control hypercalcaemia which after an initial period of control with Mithramycin 15μg/kg, and a low calcium dialysate, was controlled with the minimum possible dose of prednisolone (7–15mg daily). In the last six months serum alkaline phosphatase has risen steadily to 700iu/L, and the patient has suffered collapse of several vertebrae with fractures of 12 ribs, the right scapula and both pubic rami without any trauma.

Case 2

A woman aged 50 with renal failure from chronic glomerulonephritis was started on chronic ambulatory peritoneal dialysis (CAPD). After five months there was transient hypercalcaemia, which regressed within six weeks, but returned 15 months later and persisted for four months until she was transplanted. She collapsed two vertebrae. Despite excellent graft function for six months (serum creatinine 100μmol/L) hypercalcaemia recurs when prednisolone is reduced below 20mg/day. There is now diffuse wedging of many vertebrae and severe back pain is her major disability. Bone biopsy showed no osteitis fibrosa: the appearances were similar to those of case 1, but the aluminium stain was negative.

Case 3

A 40 year old female with analgesic abuse and possible primary hyperparathyroidism started haemodialysis. Two months later a parathyroid adenoma and three suppressed parathyroid glands were removed. Serum calcium concentration fell to normal but after 15 months became elevated. Parathyroid hormone was not detectable in her serum by either 'N' or 'C' terminal assays. For 12 months normocalcaemia was maintained with prednisolone 4–6mg daily, but subsequently serum calcium has remained normal without treatment. Bone biopsy was not performed. Within one month of hypercalcaemia developing the treatment of water for dialysate preparation was changed from a water softener to reverse osmosis.

Serum aluminium concentration in case 3 was 130μg/L when hypercalcaemia developed, and had fallen to 48μg/L when hypercalcaemia ceased. Unfortunately we do not have early estimations of serum aluminium in cases 1 and 2 as we were not routinely studying peritoneal dialysis patients at that time. Case 1 has subsequently had serum aluminium concentrations as high as 250μg/L although this

fell to 70μg/L with intensive dialysis. Serum aluminium concentration in case 2 was measured three months after transplant when despite persistent hypercalcaemia it was only 10μg/L. Case 1 had never taken more than one Alucap (475mg aluminium hydroxide) daily and cases 2 and 3 never more than three Alucaps daily.

Discussion

Three patients on different forms of maintenance dialysis developed idiopathic steroid-responsive hypercalcaemia with poor calcium absorption, progressive demineralisation of the skeleton, and two had fractures and severe clinical problems. There was no radiological or histological evidence of hyperparathyroidism and serum parathyroid hormone concentrations were low. It is likely that the apparent brief response of hypercalcaemia to transplantation in Johnson's third patient [1] was a response to steroid administration.

The cause of hypercalcaemia remains unknown. It is unlikely that there was a pre-existing cause which was unmasked by lowering of phosphate and treatment of uraemia, as there was a long delay between the onset of dialysis and appearance of hypercalcaemia, and on many occasions the patients had a high serum phosphate without improvement of serum calcium. There was no deficiency in serum calcitonin. Serum calcitonin concentrations have often been reported high in patients with renal failure [3, 4] although much of this elevation may be due to retention of inactive fragments of hormone. We have measured serum calcitonin concentration in 57 patients with terminal renal failure. If the serum is first passed down an adsorption column of sepharose coated with anti-rabbit calcitonin serum the calcitonin concentration measured in normal people is reduced by about 40 per cent. Before adsorption all our renal patients had very high serum calcitonin values, but adsorption reduced these often by as much as 80 per cent such that 35 (67%) of the patients fell within the normal range. Case 2 was normal, but cases 1 and 3 had elevated serum calcitonin on many estimations, case 3 having the highest recorded in any of our patients.

The histological osteopenia with osteomalacia and suppression of osteoblast activity is similar to aluminium induced disease. Although aluminium intoxicated uraemic patients have not been reported as becoming spontaneously hypercalcaemic, they readily develop hypercalcaemia when treated with vitamin D derivatives [5] and a group of patients acutely intoxicated with aluminium when contaminated CAPD dialysate was used developed a mean rise in serum calcium without overt hypercalcaemia [6]. It seems likely that the disease in our patients was caused by aluminium or some similar toxin. The persistence of hypercalcaemia after transplantation is compatible with this if, like aluminium, the toxin is firmly tissue bound and difficult to remove.

It is difficult to interpret the serum aluminium estimations from our patients. One would not expect symptoms of aluminium intoxication with serum aluminium concentrations below 90μg/L [7], severe symptoms usually developing in patients with concentrations above 200μg/L. Improvement of case 3 coincided with a fall in serum aluminium from 130μg/L to 48μg/L, but the change in water treatment at this time would have caused changes in concentrations of many other possible

toxins. In case 2 hypercalcaemia persisted despite a serum aluminium concentration of only 10μg/L post transplantation. It normally takes up to two years for serum aluminium concentrations of intoxicated patients to return to normal after transplantation [8]. No aluminium was detectable in the bone biopsy of case 2. Case 1 undoubtedly had toxic serum concentrations of aluminium although relatively small amounts were present in her bone biopsy and it is not clear whether the aluminium was a causative factor in her disease. It seems likely that these patients have been damaged by a toxin with similar effects to aluminium.

The low calcium absorption suggests the excess calcium is released from the skeleton, so we did not control hypercalcaemia with low calcium dialysate as this would accelerate skeletal decalcification. We suppressed serum calcium with prednisolone hoping that the benefits of reducing calcium release from the skeleton would overcome the possible harmful effects of steroid osteoporosis.

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