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Hyperphosphataemic rickets: a new variant

The biochemical abnormalities characteristic of rickets and osteomalacia are subnormal plasma calcium and phosphate concentrations. We report on two patients who presented with clinical rickets and osteomalacia who had considerably raised plasma phosphate concentrations.

Case reports

Case 1—A 19 year old vegetarian Asian man presented with weakness of his legs, especially after exercise. He also had tingling in his hands and face and cramps in both hands. His wrists were swollen and slightly tender; the tibias were bowed and tender to pressure. Proximal muscles were weak in all limb girdles. *X* ray films showed changes compatible with rickets.

Case 2—A 19 year old vegetarian Kenyan Asian woman presented with severe intermittent carpopedal spasms associated with tingling and numbness in the hands and round the mouth. She was small in stature and had generalised bony tenderness, and pronounced proximal myopathy.

Samples of plasma from the two patients were analysed biochemically. The table shows the results. Persistent hyperphosphataemia and limited phosphate excretion were noted. Responses of the patients to exogenous parathyroid hormone were therefore tested to eliminate the possibility of pseudohypoparathyroidism. An intravenous injection of 200 units (Medical Research Council) of bovine parathyroid hormone induced 60-fold and 50-fold increases in urinary excretion of cyclic adenosine monophosphate in cases 1 and 2 respectively and five-fold and eight-fold increases respectively in urinary excretion of phosphate.

Both patients were treated with calciferol 500 IU daily (as calcium and vitamin D tablets). Plasma calcium concentrations increased and phosphate concentrations and alkaline phosphatase activities fell. Bone pains and myopathy resolved.

Comment

These patients had hyperphosphataemia with severe hypocalcaemia, extremely low urinary calcium excretion, considerably raised serum alkaline phosphatase activities and parathyroid hormone concentrations, undetectable vitamin D concentrations, and radiological evidence of rickets. Small doses of calciferol, normally effective in healing nutritional rickets and osteomalacia but not hypoparathyroidism or pseudohypoparathyroidism, reversed the abnormalities in these patients. Clearly, these patients had developed an unusual biochemical presentation of severe vitamin D deficiency. Primary hypoparathyroidism was excluded because of the considerable increase in parathyroid hormone concentrations, and pseudohypoparathyroidism was excluded because of the prompt response to small doses of vitamin D and the increase in urinary excretion of cyclic adenosine monophosphate and phosphate after injection of parathyroid hormone.

As the size of the increase in urinary cyclic adenosine monophosphate and phosphate concentrations was in the low normal range the possibility that the renal response to parathyroid hormone in these patients may have been diminished, as originally suggested by Rasmussen *et al*,[1] must be considered. Lewin *et al*[2] showed a diminished response of cyclic adenosine monophosphate to parathyroid hormone in vitamin D deficiency, although none of their patients had hyperphosphataemia. Low calcium and increased parathyroid hormone concentrations in patients deficient in vitamin D may also be responsible for diminished responsiveness to exogenous parathyroid hormone.[2 3] Pronounced hyperphosphataemia, however, in association with relative hypophosphaturia in our patients reflected an almost total absence of effect of endogenous parathyroid hormone, which was considerably increased. This raises the possibility that endogenous parathyroid hormone may have altered biological activity.

After small doses of calciferol plasma calcium concentrations increased and phosphate concentrations fell. Vitamin D may therefore have a role in restoring the sensitivity of the kidney to parathyroid hormone. This effect might be either a direct one or one mediated through an increased concentration of calcium. It is relevant that the mammalian kidney has receptors to 1,25-dihydroxy vitamin D.[4]

Three siblings of one patient (case 2) had low calcium and phosphate concentrations, whereas a sibling of the other patient had hyperphosphataemic osteomalacia. Such a divergence argues against the influence of genetic factors in the pathogenesis of this form of osteomalacia.

This study shows that hyperphosphataemia may occur with florid rickets; that vitamin D may regulate the sensitivity of the kidney to parathyroid hormone; and that small doses of calciferol in this condition not only treat rickets but also reverse hyperphosphataemia.

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Results of biochemical analysis in the two patients and in siblings before and after treatment with calciferol (normal ranges given in parenthesis)

	Calcium (mmol/l) (2·1-2·6)		Phosphate (mmol/l) (0·7-1·3)		Alkaline phosphatase (IU/l) (<130)		25-hydroxy vitamin D (nmol/l) (15-45)	Urinary calcium (mmol/24 h) (2·5-7·5)	Urinary phosphate (mmol/24 h) (16-32)	Parathyroid hormone (ng/ml) (<120)	
	Before	After	Before	After	Before	After				Before	After
Case 1	1·22	2·50	1·66	1·16	600	137	7·5	0·1	14	1000	120
Case 2	1·29	2·43	1·62	1·32	540	122	7·5	0·3	1	630	120
Sibling (case 1)	1·98		1·68		335		7·5	0·2	16	730	
Sibling (case 2)	1·67		0·6		641		7·5	0·3	8	680	
Sibling (case 2)	1·82		0·68		445		10·0	0·3	9	542	
Sibling (case 2)	2·10		0·80		386		10·0	0·2	12	480	

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml. Phosphate: 1 mmol/l ≈ 3·1 mg/100 ml. 25-hydroxy vitamin D: 1 nmol/l ≈ 0·4 ng/ml. Urinary calcium: 1 mmol/24 h ≈ 40 mg/24 h. Urinary phosphate: 1 mmol/24 h ≈ 31 mg/24 h.