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Patient Report

Hyperparathyroidism and cervical canal stenosis in twins with hypophosphatemic rickets

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Familial X-linked dominant hypophosphatemic rickets (XLHP) is a common inherited metabolic bone disease with an approximate incidence of 1 per 20 000 population. Appropriate long-term treatment is problematic.[1,2] Calcific spinal canal stenosis has been described in 12 previous patients with this condition.[3–5] Standard management has been phosphate supplementation, but some patients have been reported to develop tertiary hyperparathyroidism, which may or may not be related to the use of phosphate.[6,7] The combination of tertiary hyperparathyroidism and spinal canal stenosis in the same patient has not been previously reported.

We describe a set of non-identical female twins who developed cervical spinal canal stenosis and tertiary hyperparathyroidism at similar times.

Twins A and B were born in 1951. They first presented at the age of 5 with bilateral knock-knees. In the family, their grandmother, mother and uncle on their mother's side and their older sister were affected to varying degrees of severity, but all with hypophosphatemia. Between the ages of 5 and 25 years numerous osteotomies were undertaken to reduce deformity (63 orthopaedic operations in twin A and 46 in twin B). At the age of 30, the twins were first at the Royal Adelaide Hospital.

The heights of twins A and B, respectively, were 146 cm and 148 cm. Both had normal secondary sexual characteristics with regular menstruation, frontal bossing and genu valgum.

Serum phosphate (range 0.80–11.45 mmol/L in adults) was 0.54 mol/L in both twins off treatment. Serum calcium was normal (2.3 and 2.2 mmol/L in twins A and B, respectively; reference interval, 2.1–2.55 mmol/L). Phosphate loading was performed with 1 g neutral phosphate, which increased the serum level 1 h after oral ingestion to 0.84 mmol/L in twin A and 0.78 mmol/L in twin B. The addition of calciferol to the phosphate did not increase serum phosphate values. A bone biopsy in twin A showed 'Haversian systems enlarged, containing fibrous tissue, normal osteoclastic activity and thick lamellae. The pattern resembled osteitis fibrosa more than osteomalacia' (Burnet, 1970). A diagnosis of X-linked hypophosphatemic rickets was made on the basis of the family history, with a predominance of affected females, elevation of phosphate levels with phosphate supplementation and normocalcemia.

In twin A, long-term compliance with phosphate supplements was variable. The phosphate was stopped and 1,25(OH)-2vitamin D (calcitriol) 1 μg was added. On this dose, her serum phosphate levels remained on the lower end of the normal range.

Her general health remained satisfactory until the age of 40, when she developed paresthesias in the upper limbs. X-rays of the neck revealed cervical canal stenosis. Magnetic resonance imaging (MRI) showed cervical cord compression (Fig. 1a,b) and calcification of the ligamentum lava. The patient underwent cervical decompression and laminectomy of C2–C6. Post-operatively she developed a quadriparesis, which slowly improved. A disabling fixed cervical kyphosis was a residual feature. Magnetic resonance imaging of the lumbar spine showed lumbar canal stenosis, which is asymptomatic.

At the age of 43, hypercalcemia was noted and the calcitriol stopped. Serum calcium remained elevated at 2.66 mmol/L (range 2.1–2.55 mmol/L). Serum parathyroid hormone (PTH) was 18 pmol/L (range 1–7 pmol/L). One year later, she passed a renal calculus. Ultrasonography performed at this time showed bilateral speckled calcification of the kidneys, consistent with nephrocalcinosis. She has refused any further investigations and treatment.

A similar clinical picture occurred in twin B. Magnetic resonance imaging of the cervical spine showed cervical canal stenosis and she underwent spinal canal decompression at the age of 43 without any residua. Hypercalcemia of 2.61 mmol/L was noted and a PTH of 6.3 pmol/L. She has similarly refused any further treatment. Blood for DNA

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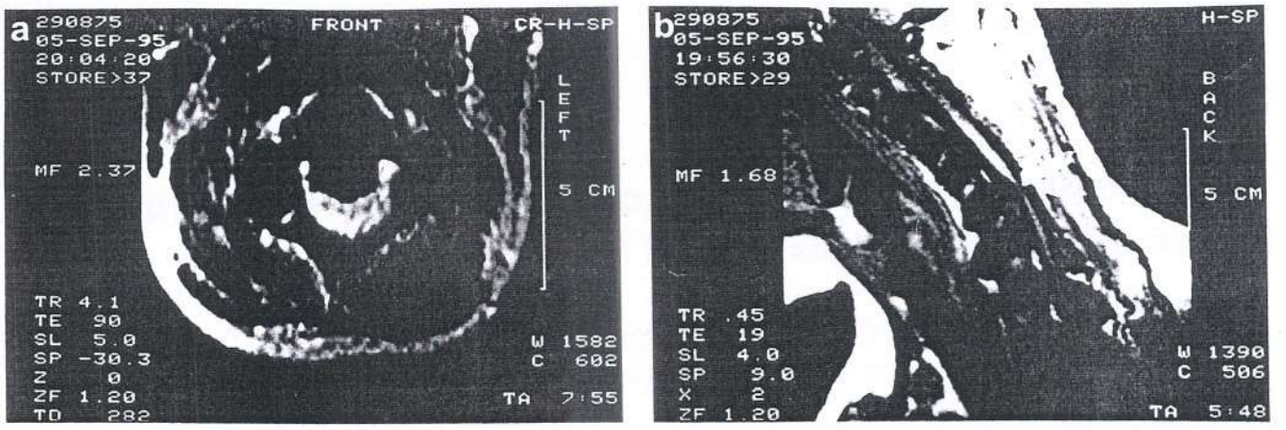

Fig. 1 (a) Magnetic resonance imaging (MRI), transverse cut through the cervical spine showing calcification of the ligamentum flavum. (b) T1-weighted MRI of the cervical spine showing compression of the cervical spine at C5–6 level in twin A.

analysis to look for known mutations yielded negative results in all three sisters.

X-linked hypophosphatemic rickets is the commonest inherited cause of rickets.[1,2] The gene has been mapped to Xp22.1–22.2 and cloned with the name *PEX* (phosphate-regulating neutral endopeptidase on X chromosome).[3,8] In this case of twins, no abnormality from the Xp22.1 locus could be isolated.

The spinal canal stenosis may be due to three possible causes: (i) facet joint hypertrophy; (ii) thickening of the vertebral laminae; or (iii) calcification of the ligamentum flavum.[4,5] The twins had predominant involvement of the ligamentum flava of the cervical spinal region. Previous series have described the age of onset of this complication ranging from 24 to 60 years with a mean age of 48 years.[4]

Hyperparathyroidism in patients with hypophosphatemic rickets has been postulated as being induced by phosphate therapy, which induces chronic stimulation of PTH secretion.[9] There is persistent elevation of the nocturnal PTH levels in some patients and this needs to be looked for to establish its presence. One of the twins received phosphate supplements, although the amount taken was suboptimal for most of the time. The other twin never took phosphate, owing to gastro-intestinal intolerance with persistent diarrhoea.

The fact that both the twins developed hypercalcemia almost within the same time frame is suggestive that an alternative mechanism precipitated hyperparathyroidism. So also is the symptomatic occurrence of spinal canal stenosis, which may indicate a genetic link for the spinal canal narrowing.

Early therapy with phosphate supplementation alone did not prevent the onset of devastating complications late in life in the present patients, nor did it prevent the frequency of corrective orthopaedic operations. With increasing longevity in patients with hypophosphatemic rickets, more appropriate therapy would be 24,25-dihydroxyvitamin D, which is a potent suppressant of PTH production.[10]

We recommend that clinicians be aware of the problem of spinal canal stenosis from the third decade onwards and screen for this to prevent devastating neurologic complications.

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