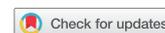


## Rickets mimicker: a report of two cases of primary hyperparathyroidism in adolescence

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The presentation of primary hyperparathyroidism (PHPT) in most Western countries has evolved from the classic description of 'stones, bones, and groans' to becoming increasingly asymptomatic as a result of more frequent serum calcium screening. However, many developing countries are still reporting predominantly symptomatic PHPT with the classic complications of skeletal disease and nephrolithiasis still being quite common. Furthermore, the exact prevalence of PHPT in children is not known but it is thought to be uncommon and the clinical presentation and outcomes in this subgroup of patients are not well described in the literature. Two cases of PHPT occurring in adolescent boys are reported. Both cases initially presented with chronic bone pain involving the lower limbs and had a long delay before the diagnosis of PHPT was confirmed. They developed progressive deformities of the lower limbs, which resembled rickets clinically. Radiological features were also suggestive of rickets. However, biochemistry confirmed parathyroid hormone mediated hypercalcaemia in both cases and after parathyroid surgery a parathyroid adenoma was confirmed histologically as the aetiology of hypercalcaemia. Therefore, PHPT occurring in adolescence may have a clinical presentation almost identical to that of rickets. All patients presenting with skeletal deformities including a rickets phenotype must have serum calcium and phosphate levels measured as part of the diagnostic workup.

**Keywords:** children, hormone-mediated hypercalcaemia, PHPT, primary hyperparathyroidism, South Africa

### Introduction

Primary hyperparathyroidism (PHPT) is a relatively common endocrine disorder with a reported incidence of 21.6 per 100 000 in some populations.<sup>1</sup> The presentation may vary among different populations. In most Western countries the disease has evolved from the classic description of 'stones, bones, and groans' by Fuller Albright and others in the 1930s, and is becoming increasingly asymptomatic as a result of more frequent serum calcium screening and hence earlier diagnosis.<sup>2</sup> Many developing countries including South Africa still encounter patients with symptomatic PHPT with the classic complications of skeletal disease and nephrolithiasis.<sup>3</sup> The exact prevalence of PHPT in children is not known but it is thought to be uncommon and the clinical presentation and outcomes in this subgroup of patients are not well described in the literature. In an earlier report from our institute almost 40 years ago, Seedat *et al.* reported on a 15-year-old boy with hyperparathyroidism associated with rickets.<sup>4</sup> In this report we present two adolescent patients with PHPT that were peculiar and similar in presentation with predominant skeletal manifestations resembling rickets.

### Case 1

A 17-year-old adolescent male was referred by an orthopaedic unit at a district hospital for investigation of possible metabolic bone disease. The patient reported that he had been well until three years before this admission when he noted pain in both hips after athletics training at school. He was able to walk and run at that time, but the pain then progressed to involve the knees and ankles over the subsequent weeks. Three months later he noted a deformity of the knees and sought medical attention from the local general practitioner (GP) who prescribed analgesia and referred him to the district hospital for genu valgus. He was followed up as an outpatient for a year

and the genu valgus progressively worsened to the point where he experienced difficulty with walking. Investigations performed at that time were not available except for a 1,25 dihydroxy-vitamin D level of 138,4 pmol/l (range 48–108.1 pmol/l) and an elevated parathyroid hormone (PTH) level of 67.9 pmol/l (range 1.7–6.5 pmol/l). His disability became significant enough to prevent him from walking unaided and he stopped schooling as a result. A year later he was admitted to the orthopaedic ward and bilateral osteotomies were performed. Both lower limbs were in plaster casts for three months and he developed fixed flexion deformities of both knees. Subsequent follow-up revealed mal-union at the site of osteotomies and he was referred to the Endocrinology Department at Inkosi Albert Luthuli Hospital (IALCH).

Further inquiry revealed no family history of rickets or other medical conditions and he had a twin brother who was well. Clinical examination revealed proportionate short stature with a height of 131 cm and weight of 43 kg; Z-scores were –5.5 and –3.0 respectively. There were no dysmorphic features and he had delayed secondary sexual characteristics with a Tanner stage 2 appearance. Musculoskeletal examination revealed pectus carinatum, Harrison's sulcus, kyphoscoliosis and rachitic rosary, suggestive of rickets. He had bilateral fixed flexion deformities of the knees with genu valgum on the right and he was unable to stand without assistance (Figure 1a–b). Systemic examination was normal. The working diagnosis was that of rickets, proportionate short stature and delayed puberty.

Biochemical investigations revealed an unexpected hypercalcaemia with a corrected serum calcium of 3.02 mmol/l and an elevated PTH level of 134.6 pmol/l in keeping with PTH mediated hypercalcaemia (Table 1). Gonadotropins and testosterone were appropriate for the Tanner stage (FSH 3.58 mIU/



**Figure 1:** (a and b) (Case 1): bilateral fixed flexion deformities of the knees and right genu valgum. (c and d) (Case 2): windswept deformity of the lower limbs with left genu valgum and varus deformity of the right knee.

**Table 1:** Laboratory results baseline and post-parathyroidectomy in index patients\*

Item	Case 1		Case 2	
	Baseline	Postoperative	Baseline	Postoperative
Ca <sup>2+</sup> (mmol/l)	3.02	2.1	3.4	2.41
PO <sup>4-</sup> (mmol/l)	1.44	1.7	0.97	0.62
PTH (pmol/l)	134.6	0.9	131.4	<0.3
ALP (IU/L)	929	941	1193	1262
Creat (μmol/l)	33	40	30	32
eGFR (ml/min)	90	88	98	95
24hr urine Ca <sup>2+</sup> (mmol/24 h)	6.1	–	5.25	–

\*Definitions (normal reference range): Ca<sup>2+</sup> = serum calcium (2.15–2.55 mmol/l); PO<sup>4-</sup> = serum phosphate (0.65–1.2 mmol/l); PTH = serum parathyroid hormone (1.5–6.5 pmol/l); ALP = serum alkaline phosphatase (50–105 IU/L); Creat = serum creatinine (30–90 μmol/l); eGFR = estimated glomerular filtration rate (mls/min); 24hr urine Ca<sup>2+</sup> = 24 h urine calcium (1–7 mmol/24 h).

ml, LH 1.8 mIU/ml, testosterone 8.6 nmol/l). Radiological findings included the following: enlargement of the anterior ends of the ribs in keeping with rachitic rosary; diffuse osteopenia with bilateral fractures of the metaphyseal regions of the femur and callus formation suggesting some healing (Figure 2a); widened non-ossified growth plates with fraying, splaying and mild cupping of the metaphysis of the distal radius and ulna suggestive of rickets (Figure 2c); mild scoliosis of the upper thoracic spine. Sestamibi scan of the parathyroid glands showed features of a large left inferior parathyroid adenoma. Bone mineral density (BMD) revealed Z-scores of –5.0 at the hip and –4.9 at the spine.

Successful left parathyroid adenomectomy revealed an adenoma that weighed 3.5 g and which was shown on histology to be benign. However, his postoperative course was complicated by the development of hypocalcaemia and hungry bone syndrome (HBS), which required repeated doses of intravenous calcium replacement over the subsequent 10 days. Postoperative PTH level was 0.9 pmol/l. At follow-up a month later, he remained eucalcaemic on 1- $\alpha$ -calcitriol 4ug daily and oral calcium 1 g bd. His clinical response was dramatic with improvement in skeletal deformities over the following year such that he was able to walk unaided and returned to school (Figure 2b, d).

### Case 2

A 13-year-old boy who was previously well developed right ankle pain, which responded to simple analgesia. Two months later the pain worsened to involve both legs and his mother noted a curvature to his lower limbs. This prompted a visit to

the local hospital where he was managed symptomatically with analgesics. Noting that the pain was unremitting, his mother sought assistance at another district hospital where investigations were commenced and he was subsequently referred to the Department of Endocrinology at IALCH with suspected rickets. Further inquiry from the mother revealed that he achieved good grades at school and actively participated in sports. There was no family history of a genetic disorder or rickets. He had normal developmental milestones until six months prior to presentation and had a normal diet including dairy products.

Clinical examination revealed no evidence of facial dysmorphism with a normal weight and height; weight 44.5 kg and height 154 cm with Z-scores of –0.15 and –0.31 respectively. Musculoskeletal examination showed windswept deformity of the lower limbs with genu valgus deformity of the left and varus deformity of the right knee (Figure 1c–d); however, there was no evidence of frontal bossing, rachitic rosary or Harrison's sulcus. Wasting of the quadriceps was noted with power in the proximal lower limbs reduced at 4/5; the rest of the neurological exam was normal. Examination of other systems was normal.

Blood tests revealed marked hypercalcaemia with a corrected serum calcium 3.4 mmol/l and an elevated serum PTH 131.1 pmol/l confirming PTH mediated hypercalcaemia. The 24 h urinary calcium excretion was 7.5 mmol/24 h. The radiological features included the following: splaying of the proximal and distal tibial metaphyses suggestive of rickets (Figure 3a); right distal fibular lucent lesion in keeping with a large Brown's tumour; splaying and flaying involving the metaphyses of the



**Figure 2:** (a and b) Knee X-rays of Case 1 before and after parathyroid surgery; (a): *before surgery*: diffuse osteopenia and bilateral femoral fractures of the metaphyseal regions with callus formation (thick arrow); (b): *after parathyroid surgery*: healing of fractures; (c and d) Hand X-rays of Case 1 before and after parathyroid surgery; c: *before surgery*: shows widened non-ossified growth plates with fraying (arrow), subperiosteal resorption of the distal phalanges (arrow), splaying and mild cupping of the metaphysis of the distal radius and ulna suggestive of rickets; d: *after parathyroid surgery*: resolution of the radiologic abnormalities.

distal radius and ulna bilaterally as well as subperiosteal resorption of the distal phalanges; typical salt-and-pepper appearance with multiple lucent areas throughout the skull vault; 'rotting fence-post appearance' on pelvic X-ray (Figure 3b). Bone mineral density (BMD) scan demonstrated a Z score of  $-2.4$  at the hip and  $-4.8$  at the lumbar spine. Sestamibi scan of the

parathyroid glands showed an increased focal uptake on the right side suggestive of a unilateral parathyroid adenoma.

He underwent focused parathyroidectomy under local anaesthesia with a right unilateral neck exploration. A large right superior parathyroid gland was resected. Intravenous calcium



**Figure 3:** (a) (Case 2): Metaphyseal changes and cortical thinning of the proximal femur giving a 'rotting-fence-post appearance' resembling rickets; (b) (Case 2): splaying of the distal tibial metaphyses (thin arrow) and a right distal fibular lucent lesion in keeping with a Brown's tumour (thick arrow).

supplementation was commenced immediately post-surgery, but despite this pre-emptive intervention he developed hypocalcaemia and latent tetany on day 2 post-surgery when the calcium infusion was tapered. Postoperative PTH levels were undetectable (<0.3 pmol/l). Histology confirmed a benign parathyroid adenoma. Large quantities of intravenous calcium were needed for seven days to maintain eucalcaemia, in keeping with HBS. Oral 1-alpha-calcidol dose was progressively increased and he was discharged on a dose of 1.5 µg bd and oral calcium 1 g bd. At follow-up 1 month later he remained eucalcaemic with no evidence of bone pain.

## Discussion

The diagnosis of PHPT in these two patients was straightforward with classical hypercalcaemia and concomitant elevated PTH level being present. Despite the typical and classic biochemical profile of PHPT in both these patients, the diagnosis was delayed either because the clinical presentation suggested rickets or as a result of the non-specific nature of the clinical presentation.

These cases highlight two important issues. First, PHPT can have a unique presentation in children with an extreme form of bone involvement leading to skeletal deformities that cannot be differentiated from the classical features of rickets. This unique type of presentation has been reported in a number of case reports of PHPT in children. There is a paucity of information on the clinical spectrum, complications and aetiology of PHPT in children due to data on this subject being limited to case reports or retrospective analysis of databases. Since prospective studies are not likely to become available due to the low frequency of PHPT in children, more meta-analyses of available studies would be helpful in clarifying the features in this subgroup of patients.

Second, it is crucial for a complete metabolic profile including serum calcium to be performed on all patients presenting with a phenotype of rickets. As demonstrated in case 1, incomplete investigation can lead to misdiagnosis and inappropriate therapy as well as worsening morbidity associated with the disease. Moreover it has been shown that vitamin D deficiency can mask the hypercalcaemia associated with PHPT and patients may actually be normocalcaemic, which may further cloud the diagnosis.<sup>5</sup> Therefore in the setting of vitamin D deficiency, serum calcium levels must also be reassessed after vitamin D replacement to exclude PHPT. In addition, presentation at a young age or the presence of severe disease should prompt consideration of genetic causes such as multiple endocrine neoplasia type 1 (MEN 1) and hyperparathyroidism-jaw tumour (HPT-JT) syndrome. Genetic testing may be warranted as PHPT can be the first presentation of MEN 1 and the mandibular lesions of HPT-JT can sometimes be occult. Lastly, these patients require long-term surveillance even if a single adenoma was detected and resected, as there may be a higher risk of recurrent disease.

PHPT in children and adolescence is more often symptomatic at presentation when compared with adults.<sup>6,7</sup> In a review of 12 studies of PHPT, Roizen *et al.* noted that only about 15% of children were asymptomatic.<sup>6</sup> However, even among asymptomatic patients most have evidence of skeletal and/or renal pathology. The presenting complaints are often vague, usually bone pain and abdominal pain. PHPT in paediatric patients is frequently delayed and has significant morbidity.<sup>7</sup> The non-specific nature of the presenting symptoms may be the reason for the delay in diagnosis and may explain the more severe disease at

presentation.<sup>6</sup> The presentation of PHPT in children is similar to that in their adult counterparts except for more severe bone disease and less severe renal disease.<sup>8</sup> Fewer than 19 cases of rickets as the presenting feature of PHPT have been reported in the literature and this seems to occur exclusively in children.<sup>5,9,10</sup> In a retrospective audit of 18 children and adolescents with PHPT, George *et al.* reported a prevalence of genu valgus of 27.8% (5 cases).<sup>8</sup> In the only other reported case from South Africa, Seedat *et al.* described the case of a 15-year-old boy who was unable to walk for years and presented with the typical clinical features of rickets including genu valgum.<sup>4</sup> In that report nutritional rickets was deemed to be the cause but also presumed to cause tertiary hyperparathyroidism; however, it is more likely that the aetiology was PHPT occurring in a child that led to the deformities.

The prevalence of HBS among children or adolescents with PHPT following parathyroidectomy has been documented in a few reports and ranges from 27.7% to 76.9%.<sup>8,11</sup> Both patients in this case report also developed HBS and had severe bone manifestations with markedly raised ALP at diagnosis. ALP levels have been shown to be significantly higher in children with documented bone involvement<sup>7</sup> similar to that noted in adults and may be a predictor for the development of HBS. Although the improvement in bone mass following parathyroidectomy in adults is well documented, the long-term outcome data in children with PHPT, particularly those with severe forms of bone disease at diagnosis, are indeed lacking. This highlights the need for further research on the outcomes of PHPT in children.

## Conclusion

Healthcare personnel need to be aware that PHPT occurring in adolescence may have a clinical presentation almost identical to that of rickets, which may lead to misdiagnosis and inappropriate therapy. All patients presenting with skeletal deformities including a rickets phenotype must have serum calcium and phosphate levels measured as part of the diagnostic workup. In patients with PHPT and extensive skeletal disease, HBS may complicate the postoperative management and this needs to be identified early and actively managed to avoid tetany. There is a definite need for more research into the clinical features, management and long-term consequences of PHPT in young patients.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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