Pseudohypoparathyroidism Type 1b; a Rare Cause of Femoral Neck Fracture

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Abstract
A 6-year-old boy was seen in general pediatric clinic for assessment of possible rickets. He had hypocalcaemia and hyperphosphatemia. Serum calcium 1.47 mmol/L, phosphorus 2.5 mmol/L and alkaline phosphatase 1957 IU/L were recorded. Radiological X-ray of the hip showed multiple lytic lesions. The diagnosis of rickets was postulated with secondary hyperparathyroidism and was started on Vitamin D3 and oral calcium. He was treated for rickets at the age of one year. Parents were consanguineous. At the age of seven years, he presented to the emergency room with left femoral neck fracture following a minimal trauma which required open reduction and internal fixation. Physical examination revealed no dysmorphic features. Biochemical investigations revealed normal complete blood count, liver and renal functions and arterial blood gas. However, serum calcium was low 2.0 mmol/L, phosphorous 2.1 mmol/L and alkaline phosphatase 1752 IU/L, serum PTH was high 1406 ng/L with normal 25 (OH) Vit. D3 and 1,25 (OH)2 Vit. D3. Pseudohypoparathyroidism (PHP) is an uncommon metabolic bone disorder characterized by biochemical hypoparathyroidism (i.e.,hypocalcaemia and hyperphosphataemia), increased secretion of parathyroid hormone (PTH), and target tissue unresponsiveness to the biological actions of PTH. In addition, many patients with PHP exhibit a distinctive constellation of developmental and skeletal defects. Pseudohypoparathyroidism type 1b can be presented as skeletal fractures. We highlight the importance of this rare cause in differential diagnosis.

Key words: Pseudohypoparathyroid, Femoral neck, Fractures

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Introduction

The term pseudohypoparathyroidism (PHP) was first described with hypocalcaemia and hyperphosphatemia due to PTH resistance rather than PTH deficiency. Affected individuals show partial or complete resistance to biologically active, exogenous PTH as demonstrated by impaired urinary cyclic adenosine 3, 5 monophosphate (c AMP), and phosphate excretion. This condition is now referred to as PHP type I. If associated with other endocrine deficiencies such as hypothyroidism and characteristic physical stigma, now collectively termed Albright’s hereditary osteodystrophy (AHO), the condition is referred to as PHP type Ia (PHP Ia). In contrast PHP type Ib, affected individuals show PTH-resistant hypocalcaemia, and hyperphosphatemia but they lack AHO. As indicated by the progressive increase in PTH concentration, PTH resistance appears to develop in patients with PHP Ia and PHP type Ib beyond the age of 1-2 years. The resistance is likely to be restricted to the proximal tubular action of PTH as affected individuals usually show diminished urinary calcium excretion, indicating that the distal tubular functions of PTH are intact. Furthermore, the osseous response to PTH remains intact and can even lead to biochemical and radiological evidence of increased bone turn over and osteoclastic bone resorption. These patients classified as PHP type I with osteitis fibrosa or pseudohypo-hyperparathyroidism.

Herein we report a case of pseudohypoparathyroidism type Ib who presented with femoral neck fracture and highlights the importance of this as a rare cause.

Case Report

A six-year old boy was seen in the general pediatric clinic for assessment of possible rickets being referred from the primary care clinic with waddling gait. He had hypocalcaemia and hyperphosphatemia, Serum Calcium of 1.47 mmol/L (Normal: 2.1-2.5 mmol/L) Inorganic phosphate 2.5 mmol/L (Normal: 0.6-1.5 mmol/L), and alkaline phosphatase of 1957 IU/L (Normal: 500-1000 IU/L). Radiological X-ray of the hip showed multiple lytic lesions mainly on the left femoral neck and greater trochanter, a picture highly suggestive of brown tumor (Figure 1).

![Figure 1: Plain X-ray of the pelvis showing multiple lytic lesions involving the femur neck and greater trochanter of the left femur (Brown tumor).](image)

The diagnosis of rickets was postulated with secondary hyperparathyroidism and put on vitamin D3 3,000 units daily and oral calcium. He was treated for rickets at the age of one year. He was a product of full term normal pregnancy with no immediate neonatal problems. Parents were consanguineous with no similar family history. He was on a normal diet and adequate sun exposure. He had no signs of liver or renal disease. His development was appropriate for his age. Review of systems was non contributory. At the age of seven years, he presented to our emergency room with left femoral neck fracture following a minimal trauma which required open reduction and internal fixation (Figure 2).
His weight was 18kg (10 percentile) and height of 112cm (25 percentile). There was no dysmorphic feature and the rest of examination was within normal. Biochemical investigations revealed normal complete blood count (CBC), liver and renal functions and arterial blood gas. However, serum calcium was low at 2.0 mmol/L (normal: 2.1- 2.5), inorganic phosphate was 2.1 (normal: 0.6-1.5), and alkaline phosphatase of 1752 IU/L (normal: 500-1000). His serum 25 - hydroxy vitamin D3 (25 [OH] vitamin D3) was 41 nmol (normal: 33-92 nmol/L ) and serum 1,25 dihydroxy vitamin D3 (1,25 [OH2] vitamin D3) was 77 nmol/L (normal: 45-160 nmol/L). Serum parathyroid hormone (PTH) level was high at 1406 ng/L (normal: 11-62 ng/L). DNA was extracted from peripheral blood leukocyte for genetic analysis from patient and parents. Methylation specific multiplex-ligation-dependent probe amplication (MS-MLPA) assay show 50% reduction in the signals of the patient but not the parents, confirming the diagnosis of pseudohypoparathyroidism type Ib of sporadic nature. Thyroid-stimulating-hormone (TSH) was 2.2 mU/L (normal: 0.5 - 5 mU/L) and free thyroxine (FT4) was 17.8 Pmol/L (normal: 10-25 Pmol/L). He was started on one-alpha 1μg twice daily and oral calcium, and after one year on therapy his serum calcium was 2.2 mmol/L, inorganic phosphate was 1.5 mmol/L, and alkaline phosphatase of 250 IU/L. The level of parathyroid hormone remains grossly elevated (240 ng/L).

Discussion

Femoral neck fractures in children are uncommon, accounting for less than one percent of all fractures in pediatric patients and most orthopedic surgeons have the opportunity to treat such fractures very few times during their career\(^9\)-\(^13\). The treatment of choice is emergency closed or open reduction and internal fixation as early as possible. In advertent delay in the fixation may occur and are not uncommon in developing countries due to a variety of reasons. These fractures are known to have a high complication rate, including osteonecrosis of the femoral neck (the most common and disabling complication) chondrolysis, non-union, premature physeal closure, coxa vara and limb-length discrepancies. Primarily, complications have been linked to delayed treatment, fracture type and patient age, inadequate reduction, and fixation failure\(^9\)-\(^13\). The cause in the majority of patients is high-energy trauma such as car accident, however, a minimal-energy trauma can induce femoral neck fracture in a previously diseased bone. Knowing the cause is important for a better outcome.

The finding of biochemical hypocalcaemia associated with hyperphosphataemia could raise the possibility of hypoparathyroidism. Furthermore, the lytic lesions on radiograph could be explained on the basis of increased production of parathyroid hormone (PTH) presumably as a result of chronic hypocalcaemia. The absence of specific dysmorphic features or mental retardation initially described by Albright’s et al and a normal thyroid function, therefore, should raise the possibility of pseudohypo-hyperparathyroidism the so-called pseudohypoparathyroidism type Ib.
Different subtypes of pseudohypoparathyroidism (PHP) seem to be related to different pathophysiologic mechanisms. In PHP type I, PTH is unable to elicit cyclic AMP (cAMP) production in target cells and administration of exogenous PTH does not increase urinary cAMP production. PHP type II is the least common form. This variant of PHP is typically a sporadic disorder, although one case of familial PHP type 2 has been reported. Patients do not have features of AHO. Renal resistance to PTH in PHP type 2 is manifested by a reduced phosphaturic response to administration of PTH, despite a normal increase in urinary cAMP excretion.

In 60% of patients with PHP type I, there is a 40% to 50% reduction in the N protein of erythrocytes, platelets or cultured fibroblasts, the N protein complies a number of membrane receptors, including that for PTH to adenylate cyclase. These patients classified as PHP type Ia, usually present with dysmorphic features described by Albright. The N protein appears to be present universally in cells, and some patients with PHP type Ia are affected by other endocrinopathies (presumably due to end-organ resistance) such as abnormal thyroid response to thyroid-stimulating hormone (TSH) and hypothyroidism, hypogonadism, and decreased cyclic AMP generation in response to glucagon. In these patients, end organ resistance appears to be progressive over the first 2-3 years of life, with dysmorphic features and possible migratory calcification preceding hypocalcaemia and elevation of serum PTH concentrations. In the PHP type IB patients the N protein contents of cells is normal and no dysmorphic features are found. In these patients, the exact molecular basis for PTH resistance is yet undetermined. A wide spectrum of skeletal or renal end-organ resistance to PTH has been reported in some patients with PHP type I. End-organ resistance is found in the kidney but the bone is normally responsive. These patients, classified as PHP type I with osteitis fibrosa or pseudohypo-hyperparathyroidism have a combination of hypocalcaemia and hyperphosphataemia with skeletal signs of hyperparathyroidism. Patient with skeletal but no renal resistance (pseudo-pseudohypoparathyroidism) present the constitutional features of PHP without hypocalcaemia or hyperphosphataemia. In these patients, skeletal defects may be more severe in the females as a result of early epiphyseal closure. In PHP type II, cyclic AMP production in urine is normally elicited by PTH, but phosphaturic response is profoundly decreased. The end-organ resistance is presumed to be due to defective tubular response to cyclic AMP. Interestingly, in these patients, restoration of normocalcaemia by treatment with Vitamin D and calcium also restores the phosphaturia response to PTH.

References

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