

Case report

Co-existence of X-Linked Hypophosphatemic rickets (XLH) and primary hyperparathyroidism. Case report and review of the literature

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Abstract

X-linked hypophosphatemic rickets (XLH) is a dominant disorder characterized by hypophosphatemia due to impaired renal tubular reabsorption of inorganic phosphate. Cardinal manifestations include defective calcification of cartilage and bone, growth retardation and resistance to phosphorus and vitamin D therapy. Although secondary hyperparathyroidism (HPT) is a common complication of treatment, autonomous HPT is rare, especially in the absence of previous phosphate therapy. We report a case of an adult untreated male XLH patient with primary HPT and give a brief review of the literature regarding the prevalence and pathophysiology of this complication.

Keywords: X-linked Hypophosphatemic Rickets (XLH), Hyperparathyroidism (HPT)

Introduction

X-linked hypophosphatemic rickets (XLH) belongs to a group of isolated renal phosphate wasting disorders, genetic and acquired, characterized by hypophosphatemia and impaired mineralization^{1,2}. XLH is caused by inactivating mutation of the cell surface metalloprotease PHEX³⁻⁵, enzyme implicated in the degradation of both phosphaturic hormones, called phosphatonins and inhibitors of mineralization, called minihibins⁶.

Hypophosphatemia can be the only manifestation of the disease, while skeletal deformities, when present, vary in degree from mild to severe⁷. Hemizygous males (X⁻Y) usually express the classic triad of hypophosphatemia, lower limb deformities and stunted growth. Characteristic laboratory findings include low serum phosphate and normal calcium concentrations, increased urinary phosphate excretion, elevated alkaline phosphatase, inappropriately normal

1,25(OH)₂D₃ and normal or slightly elevated iPTH. Radiological findings are characteristic of rickets.

Early treatment with high dose calcitriol coupled with phosphate have yielded satisfactory results concerning the correction of deformities and restoration of growth rate⁸. However these modalities should be balanced against vitamin D-induced hypercalcemia or secondary hyperparathyroidism (HPT), respectively. Although long standing secondary HPT could result in autonomous (tertiary) HPT, the presence of primary HPT in patients with XLH is rare, while the effect on bone mass and bone geometry are not reported.

Normal or slightly elevated levels of PTH are the rule in XLH. Greatly increased PTH levels as a result of hypocalcaemia caused by large doses of phosphorus are encountered as a complication of phosphorus supplementation therapy^{9,10}. Despite vitamin D supplementation, control is difficult and cases of autonomous (tertiary) hyperparathyroidism (HPT) appear that can only be treated surgically¹¹. Diffuse parathyroid hyperplasia and occasional adenomas have also been observed¹². Whether these are due to primary HPT or monoclonal expansion from diffuse hyperplasia is not clear.

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Case presentation

A 56-year-old male, with symptomatic XLH since childhood, presented with the typical physical and radiological

Serum indices (Normal Values)	Values	Urinary indices (Normal Values)	Values
Ca total (8.4-10.2 mg/dl)	10.8	Pyr-D (3.2-6.3 nM Dpd/mMcr)	9.7
Ca ionized (1.15-1.35 mMol/L)	1.43	NTX (3-51 nM BCE)	80
P (2.7-4.5 mg/dl)	1.5	cAMP neph. (0.5-4.0 nmol/dlGF)	6.8
ALP (40-129 U/L)	141	cAMP ur. (1.6-6.2 nmol/ml)	17.7
CTX (200-5800 pM)	11586	CTX (49-365 µg/mmol)	341
NTX (5.4-24.2 nM/BCE)	27.4	Ca 24h (2-4mg/kg/24h)	249 mg/24h (3.77 mg/kg/24h)
TRAP 5-β (< 5.33 U/L)	7.7	P 24h (0.4-1.3 g/24h)	1.0
iPTH (10-65 pg/ml)	388	Cr 24h (1.0-2.0 g/24h)	1.5
BGP (6.3-30.7 ng/ml)	39.1		
BAP (4.3-20.1 µg/l)	35.3		

(ALP: Alkaline Phosphatase, BGP: Bone Gla Protein, BAP: Bone Alkaline Phosphatase).

Table 1. Pre-operative biochemical indices in the serum and urine.

findings of the disease. There was positive maternal history of XLH, while his daughter was diagnosed with XLH since childhood. His son was free from the disease, compatible with the X-dominant pattern of inheritance. As a 5-year-old, he received intravenous calcium infusions and was fitted with leg braces, which he did not tolerate well and could never wear them systematically. He has never received any specific long-term therapy for his condition.

Skeletal deformities of the lower extremities, the characteristic bow legs, and growth retardation that resulted in his present short stature (1.53 m) were immediately apparent.

His presenting complaint was knee pain that began in his early twenties and has become increasingly troublesome with age. Although pain was present in both joints, symptoms were more prominent on the right side. He seeks advice about surgical treatment.

Imaging and laboratory findings

Anteroposterior and lateral X-rays of the knees and spine performed initially, reveal bilateral knee joint destruction, especially on the right side, and diffuse osteopenia. As a consequence of the latter finding, he was referred for BMD measurements of the hip and spine plus biochemical evaluation.

At the hip, femoral neck BMD was 0.615g/cm² (T-score: -3.31), a finding compatible with osteoporosis, while at the lumbar spine (L2-L4) BMD was relatively preserved (0.874 g/cm² - T-score: -2.0). Peripheral quantitative computerized tomography of the left tibia (pQCT-STRATEC XCT-2000) revealed significant reduction of vBMD at both trabecular (108.61 gr/cm³, normal values > 180 gr/cm³) and cortical sites (1118.78 gr/cm³, normal values > 1200 gr/cm³).

Laboratory testing revealed a significant increase of total and ionized calcium (10.8 mg/dl and 1.43 mmol/L respectively), high-normal urinary calcium levels (243 mg/24h), low

serum phosphate (1.5 mg/dl), with increased iPTH levels (388 pg/ml), findings compatible with primary or tertiary hyperparathyroidism. In addition, there was a significant increase in bone formation and resorption markers, such as bone specific alkaline phosphatase, osteocalcin, sCTX, sNTX, TRAP5b, urinary Pyr-D, uNTX, indicating a state of high bone turnover (Table 1). Renal function tests, thyroid and sex hormone values were within normal limits.

Radionuclide parathyroid imaging using Tc-99m-labeled 2-methoxy-isobutyl-isonitril (sestamibi) revealed a focus of uptake at the lower pole of the left thyroid lobe, suspicious for an adenoma or hyperplasia of the left lower parathyroid gland. High-resolution ultrasound examination of the neck revealed a homogenous hypoechoic nodule inferiorly to the left lower pole of the thyroid, compatible with parathyroid adenoma.

After reviewing the patient's laboratory findings and in the face of negative history of past oral phosphate therapy and normal renal function, the diagnosis of primary hyperparathyroidism was made. Given the low BMD at the femoral neck, the patient fulfilled the criteria for surgical treatment¹³. Due to the concordant findings of scintigraphy and ultrasound examination, a minimally invasive approach was recommended.

Post-operative course

In the immediate post-operative period the patient developed hypocalcemia, which was treated with oral calcium (1g/day) and alpha-calcidol (1µg/day). PTH remained slightly above normal (Table 2). Improvement of joint mobility and subsiding of knee pain were noted. Histological examination of the removed left lower parathyroid gland (weight: 0.814 gr, dimensions: 2*1*0.9 cm) revealed hyperplastic parathyroid tissue.

Parameter (normal values)	Time				
	2 weeks	6 weeks	3 months	6 months	14 months
sCa (8.1-10.4 mg/dl)	9.25	9.08	8.91	8.22	8.94
sP (2.5-4.5 mg/dl)	2.55			1.95	2.03
PTH (intact) (10-65 pg/ml)	85	65	87	72	39
ALP (98-279 U/L)					178
25(OH)D (9-52 ng/ml)				18	34
Urinary Ca 24h (2-4 mg/kg/24h)			155 mg/24h (2.34 mg/kg/24h)		252 mg/24h (3.81 mg/kg/24h)

Table 2. Serum and urine biochemical indices 2 weeks, 6 weeks, 3 months, 6 months and 14 months post-operation.

Follow-up

Three months after surgery, PTH levels were at the high-normal range, while six months post-operation PTH levels were slightly above normal, while phosphate, although low, (1.95 mg/dl), increased significantly compared with the pre-operative value. Despite this setback, the patient's clinical symptoms continued to improve. Fourteen months post-operation PTH levels were normal, phosphate remained higher (2.05 mg/dl) compared with baseline, while alkaline phosphatase was within normal limits (178 IU/L).

Discussion

The clinical manifestations of XLH are variable, ranging from isolated hypophosphatemia to severe disabling bone disease¹. The underlying mechanisms include varying degrees of defects of renal phosphate reabsorption, altered vitamin D production and/or action, intrinsic defects of osteoblastic function leading to impaired mineralization independent of hypophosphatemia⁶ and timing of implementation of optimal treatment⁸, such as phosphate salt supplementation and 1,25(OH)₂D₃ or 1 α -hydroxyvitamin D₃.

Despite low phosphate levels, several reports indicate that in both treated and untreated XLH patients, PTH levels are either normal or slightly elevated, a finding pointing to abnormal PTH production and/or secretion¹⁴. Treatment-induced PTH changes include phosphate-mediated reduction in calcium and vitamin D, possible direct stimulating action of phosphate at the parathyroid cell¹⁵, leading to secondary hyperparathyroidism and decreased vitamin D-induced inhibition of PTH secretion, due to concomitant defects in active 1,25 (OH)₂D₃ production and/or action at the parathyroid cell. Indeed, secondary hyperparathyroidism is a well established complication in XLH patients¹, which if untreated may become autonomous (tertiary)¹⁶, especially in high dose phosphate therapy¹⁰, leading to further phosphate wasting and necessitating parathyroidectomy.

Apart from the aforementioned secondary changes, several reports point to primary abnormalities in PTH secreto-

ry dynamics in patients with XLH. Carpenter et al.¹⁶ demonstrated alterations in the circadian rhythm of PTH secretion, with an exaggerated nocturnal rise of both mid-molecule and intact PTH in parallel with an increase in serum phosphate concentrations, even in untreated patients. Furthermore, there is an increasing number of reports of XLH with primary HPT^{17,18}. Although the number of reports is relatively small, the presence of HPT in untreated children and adults rises the possibility that primary defects in PTH production and secretion might be a feature of XLH. Indeed the fact that PHEX, a membrane endopeptidase, is abundantly expressed in the parathyroid gland¹⁸, sets the stage to speculate that defective PHEX function might lead to decreased PTH mRNA cleavage or PTH degradation inside or outside the parathyroid¹³. It is possible that tissue specific knock-out models may well answer this hypothesis.

In our patient's case the absence of prior phosphate therapy points to a primary defect in PTH secretion. Although histological examination of the removed parathyroid gland could not discriminate between adenoma and hyperplasia, the concordant findings of scintigraphy and ultrasound examination and the favorable post-operative course, supports the diagnosis of primary HPT due to parathyroid adenoma. However, long-term follow up is needed to secure the diagnosis.

Concerning the patient's biochemical abnormalities there was significant improvement of hypophosphatemia, a favorable effect previously reported¹⁸ in a patient with autonomous HPT following parathyroidectomy. This response underlies the adverse effects of hyperparathyroidism on renal phosphate leak. Alkaline phosphatase levels became normal, pointing to progressive healing of the bone lesions, while urinary calcium levels remained in the high-normal range. This relatively favorable response is probably the combined result of surgical treatment of primary HPT and continued vitamin D analog therapy.

While the effect of primary HPT on BMD is clearly established, with mainly catabolic effects at cortical sites and relatively preserved cancellous sites^{19,20}, the impact of XLH on BMD in both children and adults is less reported. In general, patients with XLH have reduced appendicular BMD inde-

pendent of treatment²¹⁻²³ and increased axial BMD^{22,23} caused by an overabundance of partially mineralized osteoid²² or a high prevalence of spinal osteosclerosis and enthesopathy^{23,24}. Specifically, Reid et al.²⁵ in 22 adults with XLH demonstrated that lumbar BMD was elevated above the normal range in three out of 13 as measured by quantitative computed tomography and six out of 16 as measured by dual photon absorptiometry. Regional BMD of the trunk (spine and ribs) was increased, while it was decreased in the upper and lower extremities. Hardy et al.²⁶ also provided evidence of similar discordance between the spine and extremities in adults with XLH. Equally Rosenthal et al.²⁷ using DXA for studying adults with XLH demonstrated that lumbar BMD z-scores were greater than +2 in 10 of 18 subjects. Given this background, in our patient's case there was a significant decrease of BMD in both cortical and cancellous sites assessed by both DXA and pQCT, probably reflecting the catabolic effects of HPT and the lack of previous specific treatment for XLH. It is expected that parathyroidectomy and initiation of vitamin D analog therapy will improve the patient's BMD.

In conclusion, abnormalities in PTH production and secretion are common in patients with XLH. Although the majority of patients show signs of secondary HPT related to treatment modalities, the possibility of autonomous hyperparathyroidism, either tertiary or rarely primary, should not be overlooked. More studies are needed to elucidate the prevalence and natural history of abnormal PTH regulation in XLH, the role of mutant PHEX gene in inducing HPT and the optimal interventions.

References

- DiMeglio LA, White KE, Econs MJ. Disorders of phosphate metabolism. *Endocrinol Metab Clin North Am* 2000; 29:591-609.
- Bielesza B, Klaushofer K, Oberbauer R. Renal phosphate loss in hereditary and acquired disorders of bone mineralization. *Bone* 2004; 35:1229-1239.
- The HYP Consortium. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. *Nat Genet* 1995; 11:130-136.
- Francis F, Strom TM, Hennig S, Boddrich A, Lorenz B, Brandau O, Mohnike KL, Cagnoli M, Steffens C, Klages S, Borzym K, Pohl T, Oudet C, Econs MJ, Rowe PS, Reinhardt R, Meitinger T, Lehrach H. Genomic organization of the human PHEX gene mutated in X-linked dominant hypophosphatemic rickets. *Genome Research* 1997; 7:573-585.
- Econs MJ, Friedman NE, Rowe PS, Speer MC, Francis F, Strom TM, Oudet C, Smith JA, Ninomiya JT, Lee BE, Bergen H. A PHEX gene mutation is responsible for adult-onset vitamin D-resistant hypophosphatemic osteomalacia: evidence that the disorder is not a distinct entity from X-linked hypophosphatemic rickets. *J Clin Endocrinol Metab* 1998; 83:3459-3462.
- Quarles LD. FGF23, PHEX and MEPE regulation of phosphate homeostasis and skeletal mineralization. *Am J Endocrinol Metab* 2003; 285:E1-E9.
- Favus MJ. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. Raven Press; 1993:279-282.
- Mäkitie O, Doria A, Kooh SW, Cole WG, Daneman A, Sochett E. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. *J Clin Endocrinol Metab* 2003; 88:3591-3597.
- Alon U, Newsome H Jr, Chan JC. Hyperparathyroidism in patients with X-linked dominant hypophosphatemic rickets - application of the calcium infusion test as an indicator for parathyroidectomy. *Int J Pediatr Nephrol* 1984; 5:39-43.
- Mäkitie O, Kooh SW, Sochett E. Prolonged high-dose phosphate treatment: a risk factor for tertiary hyperparathyroidism in X-linked hypophosphatemic rickets. *Clin Endocrinol (Oxf)* 2003; 58:163-168.
- Glorieux FH, Scriver CR, Reade TM, Goldman H, Roseborough A. The use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemic rickets. *N Engl J Med* 1972; 287:481-487.
- Thomas WC, Fry RM. Parathyroid adenomas in chronic rickets. *Am J Med* 1970; 49:404-407.
- Bilezikian JP, Potts JT Jr, El-Hajj Fuleihan G, Kleerekoper M, Neer R, Peacock M, Rastad J, Silverberg SJ, Udelsman R, Wells SA. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Bone Miner Res* 2002; 17(Suppl.2):N2-N11.
- Schmitt CP, Mehls O. The enigma of hyperparathyroidism in hypophosphatemic rickets. *Pediatr Nephrol* 2004; 19:473-477.
- Silver J, Kilav R, Naveh-Manly T. Mechanisms of secondary hyperparathyroidism. *Am J Physiol Renal Physiol* 2002; 283:F367-F376.
- Carpenter TO, Mitnick MA, Ellison A, Smith C, Insogna KL. Nocturnal hyperparathyroidism: a frequent feature of X-linked hypophosphatemia. *J Clin Endocrinol Metab* 1994; 78:1378-83.
- Knudtzon J, Halse J, Monn E, Nesland A, Nordal KP, Paus P, Seip M, Sund S, Sodal G. Autonomous hyperparathyroidism in X-linked hypophosphatemic. *Clin Endocrinol* 1995; 42:199-203.
- Blydt-Hansen TD, Tenenhouse HS, Goodyer P. PHEX expression in parathyroid gland and parathyroid hormone dysregulation in X-linked hypophosphatemia. *Pediatr Nephrol* 1999; 13:607-611.
- Bilezikian JP, Brandi ML, Rubin M, Silverberg SJ. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. *J Intern Med* 2005; 257:6-17.
- Bilezikian JP. Bone strength in primary hyperparathyroidism. *Osteoporos Int* 2003; 14 (Suppl.5): S113-S117.

21. Block JE, Piel CF, Selvidge R, Genant HK. Familial hypophosphatemic rickets: bone mass measurements in children following therapy with calcitriol and supplemental phosphate. *Calcif Tissue Int* 1989; 44:86-92
22. Oliveri MB, Cassinelli H, Bergadà C, Mautalen CA. Bone mineral density of the spine and radius shaft in children with X-linked hypophosphatemic rickets. *Bone Miner* 1991; 12:91-100.
23. Baroncelli GI, Bertelloni S, Ceccarelli C, Saggese G. Effect of growth hormone treatment on final height, phosphate metabolism, and bone mineral density in children with X-linked hypophosphatemic rickets. *J Pediatr* 2001; 138:236-243.
24. Polisson RP, Martinez S, Khoury M, Harrell RM, Lyles KW, Friedman N, Harrelson JM, Reisner E, Drezner MK. Calcification of entheses associated with X-linked hypophosphatemic osteomalacia. *N Engl J Med* 1985; 313:1-6.
25. Reid IR, Murphy WA, Hardy DC, Teitelbaum SL, Bergfeld MA, Whyte MP. X-linked hypophosphatemia: skeletal mass in adults assessed by histomorphometry, computed tomography, and absorptiometry. *Am J Med* 1991; 90:63-69.
26. Hardy DC, Murphy WA, Siegel BA, Reid IR, Whyte MF. X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. *Radiology* 1989; 171:403-414.
27. Rosenthall L. DEXA bone densitometry measurements in adults with X-linked hypophosphatemia. *Clin Nucl Med* 1993; 18:564-566.