

Hypophosphatemic osteomalacia in von Recklinghausen neurofibromatosis: Case report and literature review

Aman Gupta, Abhishek Dwivedi, Priyanka Patel, Somya Gupta

Department of Radiodiagnosis, Sri Aurobindo Medical College and Post Graduate Institute, Indore, Madhya Pradesh, India

Correspondence: Dr. Aman Gupta, 201 Dilpasand Avenue, 5/2 Manoramaganj, Indore - 452 001 Madhya Pradesh, India.

E-mail: aman_sono@yahoo.co.in

Abstract

Osteomalacia in neurofibromatosis is a rare entity and distinct from more common dysplastic skeletal affections of this disease. As a rule, it is characterized by later onset in adulthood. There is renal phosphate loss with hypophosphatemia and multiple pseudofractures in the typical cases. The hypophosphatemic conditions that interfere in bone mineralization comprise many hereditary or acquired diseases, all of them sharing the same pathophysiological mechanism-reduction in phosphate reabsorption by the renal tubuli. This process leads to chronic hyperphosphaturia and hypophosphatemia, associated with inappropriately normal or low levels of calcitriol, causing rickets in children and osteomalacia in adults.

Key words: Hypophosphatemia; neurofibromatosis; osteomalacia; von Recklinghausen disease

Introduction

Association of osteomalacia or rickets with neurofibromatosis has been documented only rarely.^[1] As a rule, osteomalacia in neurofibromatosis is characterized by later onset in adulthood, renal phosphate loss with hypophosphatemia, and multiple pseudofractures in the typical cases. The hypophosphatemic conditions that interfere in bone mineralization comprise of many hereditary or acquired diseases, all of them sharing the same pathophysiological mechanism-reduction in the phosphate reabsorption by the renal tubuli. This process leads to chronic hyperphosphaturia and hypophosphatemia, associated with inappropriately normal or low levels of calcitriol, causing rickets in children and osteomalacia in adults.^[2]

Case Report

A 43-year-old woman presented to the Orthopedic department of our institute with progressive bone pain and difficulty in walking since two years. The patient was a known case of neurofibromatosis-1, with multiple cutaneous nodules, from her early childhood. She was otherwise healthy until the age of 40 years, when she started experiencing progressive bone pain affecting her thighs, pelvis, and left forearm. In recent times, she could walk only with the help of crutches. On examination, tenderness and deformity were present in the regions of her left forearm, bilateral thigh, left knee, and leg. Multiple skin nodules were present all over her face, back, and abdomen [Figure 1]. She had diffuse bony tenderness.

Her skeletal survey revealed generalized osteopenia, coarse trabeculations, and nodular shadows in the soft tissue. In addition, a radiograph of her left forearm with elbow revealed fractures of the upper shafts of the radius and ulna [Figure 2]. A radiograph of her left knee revealed pseudofractures (Looser's zone) in the distal femur, upper shafts of the tibia/fibula and mid shaft of the fibula [Figure 3]. A radiograph of the pelvis with bilateral hips showed a deformed, triradiate pelvis, with bilateral

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symmetrical fractures of the upper shaft of the femur and pseudofractures of the inferior pubic rami [Figure 4]. The radiological features were consistent with diagnosis of osteomalacia.

The laboratory data in our institute were as follows: serum calcium was 8.7 mg/dL (normal 8.5-10.5 mg/dL). serum phosphorus was 1.5 mg/dL (normal: 2.5-4.5 mg/dL). alkaline phosphatase was 650 IU/L (normal 44-147IU/L). The 24-hour

urinary excretions of calcium and phosphorus were 98 mg/24 hours (normal: 0-300) and 440 nmol/24 hours (normal: 13-42), respectively. Her serum parathyroid hormone (PTH) and 25-(OH) Vitamin D were within normal range. On the basis of the radiological and laboratory findings, a final diagnosis of hypophosphatemic osteomalacia in a patient of von Recklinghausen disease was made.

Our patient is on regular follow-up. She has been prescribed a high dose of calcitriol and oral phosphate and in view



Figure 1: 43 yrs old, female known case of von Recklinghausen neurofibromatosis with multiple skin nodules all over her face and legs



Figure 2: Radiograph of left forearm with elbow A.P. and lateral revealed diffuse osteopenia with fractures of upper shafts of radius and ulna (arrows)



Figure 3: Radiograph of left knee with leg A.P and lateral revealed generalized decrease in bony density with pseudo fractures (Looser's zone) in the distal femur, upper shafts of tibia/fibula and mid shaft of fibula (white arrows). Note nodular shadows in soft tissue (black arrows)



Figure 4: Radiograph of pelvis-A.P. view. Triradiate pelvis with osteopenia and bilateral, symmetrical fracture of upper shafts of femur (white arrows) with bilateral, symmetrical pseudo fracture of inferior pubic rami (black arrows)

of innumerable neurofibromas, surgical resection was not advised. Her constitutional symptoms have improved, but the fractures have shown no radiological signs of healing in the last three months of follow-up.

Discussion

Oncogenic hypophosphatemic osteomalacia (OHO) is a rare endocrinological paraneoplastic syndrome, characterized by defective bone mineralization from renal phosphate loss. It is an unusual condition, but probably still is the most common cause of acquired hypophosphatemic osteomalacia in adult males.^[3] The affected age group range is between seven and seventy-seven years with a Male: Female ratio of 1.2:1. The oncogenic osteomalacia syndrome is gradual in onset. Patients characteristically present with joint deformities, waddling gait, bone pain, muscle weakness, anorexia, fatigue, and occasionally long-bone fractures. The initial clinical presentation may be mistaken for rheumatoid arthritis, muscular dystrophy or primary neurological disorder in some cases.^[4]

Oncogenic osteomalacia is almost exclusively described in patients with tumors of mesenchymal origin.^[5,6] If the biochemical profile of the patient is that seen in hypophosphatemia, namely low phosphate in the serum and high phosphate excretion in the urine, and the patient is not responding adequately to oral calcium and vitamin D therapy, then the possibility of an underlying cause of either renal or oncogenic or hereditary X-linked hypophosphatasia must be entertained. The most common tumor described is hemangiopericytoma, but other tumor types described include fibrous dysplasia, osteosarcoma, chondroblastoma, chondromyxoid fibroma, malignant fibrous histiocytoma, giant-cell tumor, hemangioma, paraganglioma, prostate cancer, and oat-cell carcinoma of the lung. Neurofibromatosis is rarely associated with oncogenic osteomalacia.^[1,3,7]

Abdel-Wanis, *et al.*^[8] hypothesize that putative melatonin deficiency in cases of neurofibromatosis-1 may play a role in the pathogenesis of hyperphosphaturia, by decreasing the sodium-phosphate cotransport, increasing the level of cyclic adenosine monophosphate (cAMP) and the un-antagonized effect of dopamine on phosphate reabsorption, and increasing the glucocorticoid levels. Parathyroid overactivity that may occur secondary to osteomalacia may have synergistic effects with dopamine and further exaggerate the phosphate loss in urine. On the other hand, excess corticosteroid secretion will decrease the nocturnal melatonin level. Moreover, in the presence of hypophosphatemia, hypercortisolism may further inhibit melatonin secretion that may lead to progression of bony deformities in these cases.

In recent times, it has been suggested that in the

epidermal nevus syndrome and type-1 neurofibromatosis, hypophosphatemic rickets/osteomalacia is probably due to increased secretion of fibroblast growth factor 23 (FGF-23) by cells from the nevus or neurofibromas.^[2] X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, tumor-induced osteomalacia (TIO), fibrous dysplasia, and the McCune Albright Syndrome share a common underlying pathophysiological condition: increased phosphorus renal loss secondary to augmented FGF-23 plasma levels and activity. These excessive amounts cannot be adequately degraded by the *PHEX* gene.^[9] (a gene on the X chromosome that codes for a Zn-metalloendopeptidase proteolytic enzyme, which regulates the phosphate). FGF-23, the largest member of the fibroblast growth factor family (FGF), contains 251 amino acids and is encoded by a gene in 12p13.^[10] It is synthesized by osteogenic cells, osteoblasts, and osteocytes. This protein exerts a regulatory role in phosphaturia^[11,12] that is being postulated as a 'phosphaturic factor,' which is also called phosphatonin. FGF-23 also inhibits renal 25(OH)-1- α -hydroxylase activity, leading to decreased calcitriol synthesis.^[11,13] This results in hyperphosphaturia, hypophosphatemia, and subsequently oncogenic hypophosphatemic osteomalacia.

The metabolic abnormalities in oncogenic osteomalacia are hypophosphatemia, hyperphosphaturia, low or normal serum calcium, raised alkaline phosphatase, low concentrations of 1,25 dihydroxy Vitamin D, decreased tubular resorption of phosphates,^[3,4,14] normal parathormone levels, and normal urinary calcium.

Dysplastic skeletal lesions are frequent in neurofibromatosis. These are believed to be the result of mesodermal dysplasia, intrinsic to the disease and they appear early in life. They cause bone deformities, and are not associated with disturbances in calcium and phosphate metabolism. In contrast, osteomalacia of neurofibromatosis is very rare, presents in middle age, and is associated with marked disturbance of phosphate metabolism. The patient presented here had no skeletal symptoms till the age of 40 years. The presence of multiple symmetrical pseudofractures (Looser's zone), high alkaline phosphatase, low serum phosphate, and generalized demineralization of the bones pointed to the diagnosis of hypophosphatemic osteomalacia.

In oncogenic osteomalacia, removal of the tumor is the treatment of choice. If complete excision of the tumor is achieved, it can lead to improvement in the clinical course of the disease as well as the biochemical markers, and may be curative.^[3] In patients with neurofibromatosis and osteomalacia, although innumerable neurofibromas are present, it is probably the largest ones or those with recent growth that cause OHO and their surgical removal should be tried, to achieve permanent cure.^[7] High doses

of calcitriol and oral phosphate salts are indicated, similar to those used in the treatment of X-linked hypophosphatemia.^[1,2,8]

Conclusion

Osteomalacia in neurofibromatosis is a very rare entity and distinct from the more common dysplastic skeletal affections of this disease, as a rule, being characterized by later onset in adulthood, with renal phosphate loss, and with hypophosphatemia and multiple pseudofractures in typical cases. In patients with neurofibromatosis, although innumerable neurofibromas are present, it is probably the largest ones or those with recent growth that cause OHO, and their surgical removal should be tried, to achieve permanent cure, along with high doses of calcitriol and oral phosphate.

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