

# A pediatric hypophosphatemic rickets on MRI, $^{99m}\text{Tc}$ -MDP bone scan and $^{18}\text{F}$ -FDG PET/CT

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## Abstract

We present a case of a 13 years old boy who was hospitalized with a 10 months history of progressive pain and weakness in his lower extremities. The laboratory tests revealed slightly decreased phosphate and 25-hydroxyvitamin D3, high alkaline phosphatase, normal calcium and parathyroid hormone (PTH). Magnetic resonance imaging (MRI) showed multiple patchy lesions indicating bone destruction in the metaphyses and epiphyses of the left knee. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG PET/CT) revealed a generalized decrease of bone density in axial bones with slightly increased  $^{18}\text{F}$ -FDG metabolism. Whole body technetium-99m methylene diphosphonate ( $^{99m}\text{Tc}$ -MDP) scintigraphy revealed multiple areas of increased uptake at costochondral junctions of the ribs bilaterally suggesting a rachitic rosary and at the metaphyses of the bones of the limbs. Based on these findings we suggested the diagnosis of hypophosphatemic rickets (HPR). Phosphate and vitamin D substitution resulted in clinical improvement of the symptoms after 3 months.

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## Introduction

Rickets is a common condition in children due to a defect in bone mineralization which leads to abnormalities of the growth plate cartilage which is predominantly observed in long bones. Rickets can be divided into calcipenic and phosphopenic [1]. Phosphopenic or hypophosphatemic rickets (HPR) is a common denominator of both groups of rickets [2]. The etiology of HPR includes the following: deficiency of vitamin D, of calcium, or phosphorus; absorption defects resulting from gastric, pancreatic, intestinal, and hepatobiliary disorders [3] and renal disorders. Disorders of renal phosphate wasting are the most common hereditary forms of HPR and are chemically manifested by hypophosphatemia, decreased renal tubular reabsorption of phosphate, decreased intestinal absorption of calcium, and normal serum calcium [1].

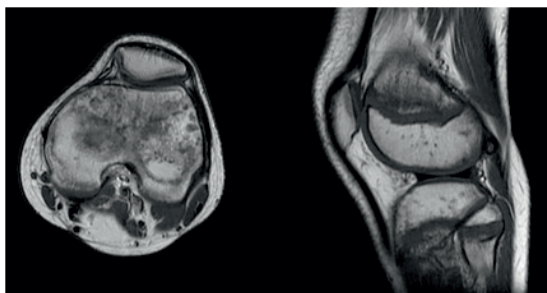
This report describes a rare case of hypophosphatemic rickets (HPR) of unknown origin with slightly low serum phosphate imaged by fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG-PET/CT), technetium-99m methylene diphosphonate ( $^{99m}\text{Tc}$  MDP) bone scanning and magnetic resonance imaging (MRI).

## Case Report

A 13 years old boy was hospitalized with a 10 months history of progressive pain and weakness in his lower extremities. He was born at full term with a normal delivery. His height and weight were 158cm and 33kg, respectively. The pain was aggravated by movements and relieved after rest. He could not go upstairs and could not walk. The illness began in his knees and spread to his ankles. Physical examination revealed no muscle atrophy. Deep tendon reflexes were positive in bilateral biceps and triceps muscles, the radial muscle and muscles of the knee and ankle. The evaluation of parathyroid function was unremarkable. Magnetic resonance imaging performed in a district hospital, showed heterogeneous signal in the bilateral sacral joints. The cervical, thoracic and lumbar MRI were normal. analgetic administrated orally did not relieve the pain. Azithromycin and antiphlogistic agents had little effect on the pain. Four months later, he was referred to

another hospital. Tests for other illnesses that could cause his pain, such as rheumatoid arthritis and ankylosing spondylitis, were negative. He also had normal phosphate and calcium. Bone marrow puncture was also negative.

The boy was then finally referred to our hospital. The laboratory results were as follows: phosphate (P) 0.75mmol/L (normal range, 0.8-1.5), calcium (Ca) 2.16mmol/L (normal range, 2.1-2.6mmol/L), alkaline phosphatase (ALP) 870U/L (normal range, 34-114U/L), parathyroid hormone (PTH) 30.01pg/mL (normal range, 15-65pg/mL), 25-hydroxyvitamin D3 (25-(OH)D3) 16.34ng/mL (normal range, >20ng/mL),  $\beta$ -C-terminal telopeptide of type I collagen ( $\beta$ -CTX) 2.18ng/mL (normal range,  $\leq$ 0.854ng/mL), total serum amino-terminal propeptide of type 1 procollagen (P1NP) 1038.00ng/mL (normal range, 17-67-96.76ng/mL for male adults), osteocalcin 73.87 ng/mL (normal range, 14-70ng/mL for male adults). Urine P was 0.36g/24h (normal range, 1.1-1.7g/24h), urine Ca 60.12 mg/24h (normal range, 50-400mg/24h). He had normal electromyogram, evoked potential and nerve conduction in the lower extremities. Magnetic resonance imaging showed multiple patchy abnormal signals indicating bone destruction in the metaphyses and epiphyses of the left knee (Figure 1). Metastatic bone lesions were suspected and the related serum tumor markers were normal. Fluorine-18-FDG PET/CT was then performed and found no hidden malignant neoplasms, but demonstrated the heterogeneous bone density at the joints of the limbs, blurred articular surface in bilateral sacroiliac joints in the knees and the ankle joints and also showed a generalized decrease of bone density in the axial bones with slightly increased  $^{18}$ F-FDG metabolism (Figure 2). Whole body  $^{99m}$ Tc-MDP scintigraphy revealed multiple areas of increased uptake at the costochondral junctions of the ribs bilaterally suggesting a rachitic rosary and also at the metaphyses of the bones of the limbs (Figure 3). The diagnosis of HPR was indicated and the boy received treatment with phosphate and vitamin 1.25-(OH) $_2$ D $_3$ . Three months later, the pain and the weakness in the lower extremities were quite relieved.

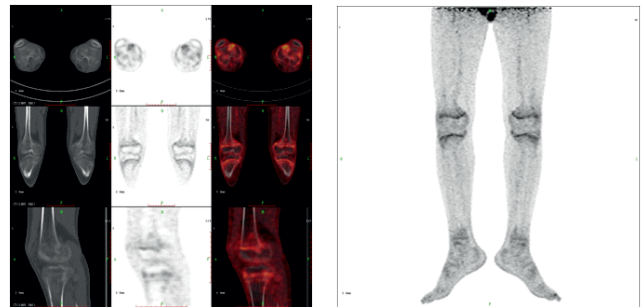


**Figure 1.** A magnetic resonance image shows multiple patchy abnormal signals indicating bone destruction in the metaphysis and epiphysis of the left knee.

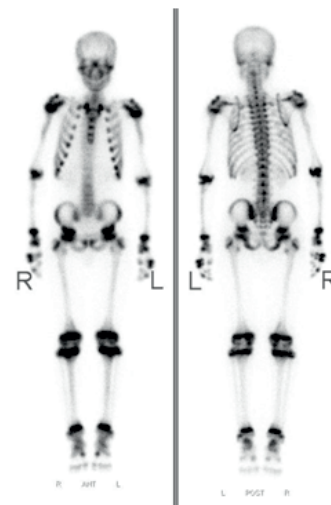
## Discussion

Hypophosphatemic rickets (HPR) is a group of disorders characterized by a defect in renal tubular reabsorption of phosphate, which causes defects in bone mineralization and hypophosphatemia. The defect in renal tubular reabsorption

of phosphate was classified into four main subtypes: X-linked HPR, autosomal dominant HPR, hereditary HPR with hypercalciuria, and tumor-induced osteomalacia [4-8]. X-linked HPR is the most common form of heritable HPR [9-11] with an incidence of 1:20,000 live births [1] which is characterized by massive phosphate wasting, which causes growth retardation, bone malformations, abnormal vitamin D metabolism, and hypophosphatemia [12]. A 16 years old female patient and her father with X-linked HPR harboring a novel PHEX mutation has been previously reported [13]. In a recent study, two novel mutations in the PHEX gene in patients with HPR were identified in India [14]. Unfortunately, a genetic test was not performed in our case.



**Figure 2.**  $^{18}$ F-FDG PET/CT demonstrated multiple osteolytic lesions in both knees with slightly increased  $^{18}$ F-FDG metabolism (SUVmax2.1).



**Figure 3.** Technetium-99m-MDP whole-body bone scan revealed multiple areas of moderately or intensely increased uptake at costochondral junctions of the ribs bilaterally suggesting a rachitic rosary and at the metaphyses of the bones of the limbs.

Tumor-induced osteomalacia (TIO) is a rare disorder of phosphate wasting due to fibroblast growth factor 23 (FGF23)-secreting tumors, that are often difficult to locate [15]. Complete surgical removal of the underlying tumor provides definitive cure. Tumor-induced osteomalacia is benign, slow growing, and mainly due to a phosphaturic mesenchymal tumor of mixed connective tissue [16] which can be located in nearly every part of the body [16-18]. These TIO

can present at any age and are accompanied with longstanding bones pain and muscular weakness [19]. Tumor-induced osteomalacia has been previously reported in a child with a central giant cell granuloma [20]. These tumors usually go undiagnosed for many years [11]. Functional imaging with indium-111-octreotide using single photon emission tomography (octreo- SPET or SPET/CT) was reported to be sensitive and specific and  $^{18}\text{F}$ -FDG-PET/CT to be complementary for the diagnosis [15]. Fluorine-18-FDG PET/CT is also useful to rule out TIO as in our case. Gallium-68 dotatate PET/CT is effective and promising for the diagnosis of TIO [21].

According to our knowledge, only an adult HPR has been reported by  $^{18}\text{F}$ -FDG PET/CT. The  $^{18}\text{F}$ -FDG PET/CT findings in that case are not the same with our findings because that case showed metabolically active marrow with multiple areas of fractures in a 34 years old female with HPR [22].

Serum levels of phosphorus, calcium and vitamin D supported the diagnosis of hypophosphatemic rickets. Pathophysiology of phosphate homeostasis may be maintained by fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and calcitriol [23]. The most important factor in the pathogenesis of HPR is FGF23 and its measurement is useful for the diagnosis of FGF23-dependent HPR [13]. However, the relationship between FGF23 and PTH remains unclear [24]. Calcitriol [1.25(OH) vitamin D] and serum phosphate is a potent physiologic stimulator of FGF23 secretion [24-26]. Most HPR patients have normal 1.25-OH vitamin D levels, low levels do not rule out HPR [23]. As showed by our case, the slightly low phosphate and 1.25-hydroxyvitamin D3 made the diagnosis of HPR possible. Our case had both low urine and serum phosphate which may be due to the low phosphate diets and low urine osmotic pressure.

Adult patients with HPR have a generalized softening of the skeleton due to defective mineralization, known as osteomalacia with muscle weakness and bone pain. In childhood, HPR is mainly presented with growth retardation and bones deformity. Our case had similar clinical features as the adults have without growth retardation and bone deformities. Hypophosphatemic rickets inhibits apoptosis in the hypertrophic cells in the growth plate. In the absence of apoptosis, the hypertrophic cells accumulate in the growth plate and form the rachitic bone [27], which is characterized by intensely increased uptake of the radiopharmaceutical in bilateral ribs (rachitic rosary) and in the metaphyses of the bones of the limbs as shown in the  $^{99\text{m}}\text{Tc}$ -MDP bone scan. As far as bone scan findings are concerned, the bone scan pattern of oncogenous osteomalacia and osteomalacia secondary to other causes is indistinguishable [28, 29]. Magnetic RI in another case showed an osteolytic lesion in the maxilla [20]. In addition, in our case MRI showed multiple patchy abnormal signals indicating bone destruction in the left knee, proximal tibia and fibula. Fluorine-18-FDG PET/CT confirmed the typical rachitic findings [20] and the multiple osteolytic lesions at the bones of the limbs with slightly increased  $^{18}\text{F}$ -FDG metabolism and ruled out malignancy. As suggested [27], our imaging findings confirmed that a radiographically generalized decrease in bone density, especially in the axial skeleton, is a characteristic finding of HPR as

shown by MRI,  $^{18}\text{F}$ -FDG PET/CT and the bone scan.

The treatment for HPR is phosphate replacement in the form of a phosphate mixture with 1.25(OH) D (or 1-OHD). Most patients have marked improvement of the bone pain as in our case. As the child progresses to adulthood, the phosphate requirements decrease due to the closure of epiphyses and to decreased bone turnover [2]. Phosphate is generally administered at 20-40mg/kg/day in three to five divided doses (up to a maximum of 2-3g/day). Calcitriol is used in doses of 1-3 $\mu\text{g}$ /day [2]. Therapy should be targeted to maintain serum phosphorus in the low normal range, normalize alkaline phosphatase, and prevent secondary hyperparathyroidism, hypercalcemia, or hypercalciuria [1]. Serum calcium, phosphorus, creatinine, and spot urinary calcium/creatinine should be monitored every 3-4 months [1]. Parathyroid hormone levels should be checked annually. Nephrocalcinosis and tertiary hyperparathyroidism are the potentially serious complications of therapy [30]. Renal ultrasound should be done at the baseline and yearly thereafter. Other therapies that have been suggested are cinacalcet and octreotide [31].

In conclusion,  $^{18}\text{F}$ -FDG PET/CT and  $^{99\text{m}}\text{Tc}$ -MDP scan were useful to rule out malignancy identify TIO and show the characteristic for rickets generalized decrease in bone density. Additionally in the axial skeleton, bone destruction and the rachitic rosary were detected. Serum levels of phosphorus, calcium and vitamin D supported the diagnosis of hypophosphatemic rickets.

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