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X-Linked Familial Hypophosphatemia: A Case Report of 27-Year Old Male and Review of Literature

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ABSTRACT

X-linked hypophosphatemia (XLH) associated with short stature during childhood are mostly referred to the hospital and diagnosed as vitamin D deficiency rickets and received vitamin D before adulthood. A case is presented with clinical features of hypophosphatemia from childhood who did not seek medical care for diagnosis and treatment, nor did his mother or two brothers, who have short statures, bone pain, and fractures. The patient was assessed for sociodemographic, hematological, and biochemical parameters together with a genetic assessment. A DEXA scan and X-ray were done to determine the abnormalities and deformities of joints and bones despite clinical examination by an expert physician. All imaging, laboratory parameters, and the genetic study confirmed the diagnosis of XLH. A detailed follow-up of his condition was performed after the use of phosphate tablets and other treatments. X-linked hypophosphatemia needs a good assessment, care, and follow up through a complementary medical team including several specialties. Phosphate tablets in adulthood significantly affects clinical and physical improvement and prevention of further skeletal abnormality and burden on daily activity. The patients should be maintained with an adequate dose of phosphate for better patient compliance. More awareness is needed in society and for health professionals when conducting medical checkups during the presence of stress fractures, frequent dental and gum problems, rickets, short stature, or abnormality in the skeleton or walking to think of secondary causes such as hypophosphatemia. Further investigations including a visit to a specialist is imperative to check for the primary cause of these disturbances.

Introduction

Phosphate homeostasis and pathophysiology of hypophosphatemia

Phosphate is a crucial component of the body, with the majority of phosphate in the human body present in the bone (85 %), most of the rest (14 %) is present intracellularly, and only < 1 % is present in the extracellular space [1]. Although it is not as tightly regulated as serum calcium, it has many beneficial effects on the body. Its chronic deficiency is associated with a significant diminish in bone mineralization. Many factors that control calcium levels are also involved in controlling serum phosphate. Although its abnormal serum level does not cause an immediate effect on the body, its chronic deficiency is associated with a significant diminish in bone mineralization [1]. Hypophosphatemia occurs when the serum phosphate level is < 2.5 mg/dl [2, 3] (normal value in the adult is 3–4.5 mg/dl) [4]. In infants and children, a higher phosphate level is necessary to prevent rickets; the normal adult value could be insufficient [4, 5], and the normal value in children is 4–7 mg/dl [4].

Hypophosphatemia develops mainly via decreased reabsorption and increased loss of phosphate through urine, which might be resulted from hyperparathyroidism [2] during chronic kidney disease or vitamin D deficiency [6]. Additionally, the urinary loss of phosphate could be caused by genetic disorders of renal sodium/phosphate co-transporters. More rarely is due to the gastrointestinal cause; malnutrition, inadequate phosphate intake, or tumor [2].

The phosphate level is controlled by the 1,25-dihydroxyvitamin D, parathyroid hormone, fibroblast growth factor-23 (FGF23), and phosphate regulating gene with homologies to endopeptidase on X-chromosome (PHEX). The sodium/phosphate co-transporter function to reabsorb phosphate from kidney tubules by phosphate transport from the kidney's proximal tubule to the blood, which is under the control of PHEX and FGF23, a substrate of this endopeptidase. These transporters are regulated by parathyroid hormone (PTH), 1,25 dihydroxyvitamin D, and dietary phosphate [4]. Both PTH and FGF23 affect the upregulation of these transporters [5]. Furthermore, FGF23 is released from osteoblasts and osteocytes and inhibits PHEX and phosphate reabsorption. Thus, any factor that raises FGF23 eventually leads to phosphate urea and hypophosphatemia [7]. Hereditary hypophosphatemia could be XLH [8], autosomal dominant [9], or autosomal recessive hypophosphatemic rickets (ARH) [10].

Epidemiology of X-linked hypophosphatemia

This rare condition is reported to have an incidence of 1 in 20 000 births. Presently, > 460 mutations related to XLH have been stated in the literature [11].

Generally, this disease is genetic and transmitted from parents to offspring; thus, it appears mostly during childhood. However, XLH with no family history of this ailment is also described in adolescents/adults [12], and many sporadic cases – 10 out of 30 cases – were also found in a comparative study by Whyte et al. [13]. XLH affects both females and males; however, in some families, it has been detected that males may have more severe sorts of disease than females [13]. There is no confirmed data in the literature to approve that XLH is related to the region/area of living/staying.

Clinical presentation

The symptoms and signs of chronic hypophosphatemia could appear from early childhood, by growth retardation, bone/joint pain, widening of the common spaces, rachitic lesion, bowing of the leg, muscle weakness, and difficulty in walking, delayed dentition/dental problems [14, 15], vitamin D resistance rickets, and frequent fractures/stress fractures. The main clinical feature of XLH in childhood is rickets, most probably falsely diagnosed as nutritional or vitamin D deficient rickets and treated accordingly [16], which could lead to lower limb deformities and short stature in the future [17, 18]. In addition, decreased bone mineralization will affect the growth plate [19] and, at the same time, increase FGF23 receptor expression in the bones, resulting in ossification in the skull [20].

The development of clinical features of this disease vary according to the severity of the mutation; some cases will not have sign and symptoms till adulthood and present with bone pain, muscle ache, stress fractures, dental problems and, affecting their quality of life [15, 21], others were even without symptoms in the adulthood [22]. Cases associated with clinical features, early diagnosis, and treatments are allied with improved consequences [23].

Clinical presentation in childhood

Most of the patients reported having short stature and bowing of legs (tibia, fibula, or both), followed by turning of the femur and genu valgum [17]. Short length in XLH appears initially in the course of the disease, and the –1.4 z-sore for height was recorded in early age in a study on children with ≤ 4 years [24], and a z-score range of – (6.5–1) was recorded in children with wider age group ≤ 18 years [25]. The discrepancy in the bone length of the legs and their defects lead to abnormality in the gait of these patients; orthopedic surgery is often needed [17, 19, 26].

Dental problems were detected in a significant number of children. For example, decreased bone mineralization and pulp enlargement due to hypophosphatemia will lead to thinning of the enamel, with more risks of dental caries, fractures, abscesses, and infection of the oral cavity [17, 19]. In addition, a craniofacial abnormality that might result in headache, vertigo, elevated intracranial pressure, or rarely papilledema [27] could be among the manifestations of XLH during childhood [19, 28].

Clinical presentation in adulthood

In adulthood, due to disease progression, the patients most probably presented with bone pain, difficulty walking, and pseudo-fractures; these manifestations are combined with short stature and other sequelae of the disease from childhood rickets [17, 29]. There is also a risk of development of enthesopathy; studies showed a more significant percentage of enthesopathy after adulthood, especially after the age of thirty; almost all of the patients have this problem which results in joint stiffness and pain, in addition to degenerative osteoarthritis and other common abnormality could develop [17, 30]. Phosphate depletion in muscles with decreased muscle activity and motion, could be responsible for the weaknesses that present in muscles of XLH patients [31, 32].

Diagnosis of X-linked hypophosphatemia

Early diagnosis/treatment initiation, satisfying management, and consistent follow-up of patients with XLH regulate their long-term

consequences and upcoming quality of life (QoL), including improved general growth and height, bone mass accrual, fewer bone deformations, and healthier dental growth [33]. Thus, medical/family history, auxology, musculoskeletal test, and proper investigation (radiology, biochemistry, and genetic studies) benefit starting the correct XLH diagnosis [12].

Diagnosis of XLH is made by low serum phosphate and phosphate urea [34], which are associated with slightly lower serum 25-hydroxyvitamin D and probably normal serum calcium. In comparison, other findings of XLH on diagnosis are somewhat elevated alkaline phosphatase (ALP) and PTH. For genetic causes, family history and pedigree help diagnose, while genetic study fully confirms the exact diagnosis.

Medical history

A thorough medical history, including family history, for starting the mode of inheritance is considered an essential task in diagnosis. Suppose one of the parents has XLH with clinical signs of XLH, such as short stature, misshapen legs, frequent scars from orthopedic surgical operations, anomalies of the skull shape with frontal bossing, and loss of permanent teeth due to persistent dental sores and periodontal infection [12]. On the other hand, the diagnosis in most cases was delayed when there was no family history of the XLH, which is described in 30 % of de novo PHEX mutations. Some adults with XLH who have milder manifestation cannot visit health care or follow up on their visit to reach the diagnosis, and sometimes the diagnosis of these adult patients are difficult; their abnormality could be failed to relate to childhood disease [35].

Physical screening

A detailed physical examination should be conducted, such as intensive auxology (head circumference, standing height/length, sitting height, and body weight) [12]. The typical and characteristic appearance in familial XLH is rickets, which displays long bone deformities, including limb bowing, late walking, waddling gait, and bone/joint aches rising gradually once toddlers start standing/walking [36]. Additionally, osteomalacia, degenerative joint disease, enthesopathy, and repeated dental sore can be observed [37]. Also, 60 % of XLH patients own dental infections of deciduous and permanent teeth due to diminished mineralization of dentine/enamel that permits bacteria to attack the pulp and results in tooth abscesses even when there is no trauma/tooth decay [38].

Radiological screening

At an early age with XLH, a radiograph of a wrist/knee shows classical radiological alterations of rickets-widening, cupping, and fraying of the metaphysis. Generally, radiological screening shows deformities principally in the lower limbs, metaphyseal widening, poor definition of bone contours, rachitic rosary, and frontal bossing [11]. Malformations in flexion of the distal diaphysis, radii, ulnas, and tibias with dorsal column worsening were also observed. Teeth radiograph of patients presents dentin with various mineralization appearance, large pulp chambers, with grey areas between anterior and posterior teeth [39].

Biochemical screening

Biochemical screening should be achieved as soon as possible after the seven days of life, including serum phosphate (low), creatinine and alkaline phosphatase (ALP, higher), urinary phosphate (wasting), and creatinine. In adult patients, the ALP could be normal or elevated [17, 40]. Additionally, screening for parathyroid hormone (PTH) (normal or upper normal range), serum calcium (normal), and urinary calcium excretion (normal) also should be done [41]. Measurements of plasma levels of both intact FGF23 and C-terminal FGF23 are also recommended when necessary to exclude some other diseases. Serum phosphate shows different ranges according to age; unfortunately, most laboratories do not show age-specific phosphate ranges, one of the factors that could result in delayed diagnosis of the disease [40].

Gene mutation

This disease is profoundly associated with inheritance and genetic causes; however, cases with no family history of XLH are also reported [12]. Therefore, to exclude other differential diagnoses associated with identical biochemical and/or clinical abnormalities, genetic testing could be necessary to aid diagnosis, although a history of the same problem in one of the family member make diagnosis more accessible, as stated in the review by Dahir et al. 2020 [17]. Approximately 90 % of XLH rickets are associated with PHEX gene mutations. The PHEX gene encodes a metalloprotease, a member of the M13 family of zinc-dependent proteases of the cell membrane type II, and is expressed in the bone, teeth, lung, ovary, testes, and parathyroid gland [11]. XLH, due to PHEX mutations, follows an X-linked dominant inheritance pattern. Thus, the affected fathers transmit the disease to their daughters and none of their sons, while affected mothers have a 50 % risk having an affected daughter/son.

Consequently, PHEX gene mutation assessment and exome sequencing are helpful and gold parameters for diagnosing this syndrome [36]. This form of hypophosphatemic rickets is the most predominant type (80 %) of familial XLH. In contrast, the rarer types are autosomal dominant, autosomal recessive, and hereditary hypophosphatemic rickets with raised urinary calcium levels [15].

Management and treatment

Conventional therapy

XLH is a life-long illness; none of the medications among conventional treatments can correct the original abnormality and cure the patient; the medications are used to improve phosphate and 1,25-hydroxyvitamin D levels and prevent further progression of skeletal and other clinical abnormalities, and better life quality [42].

The conventional treatment of this condition is the active form of vitamin D3; calcitriol or vitamin D analogues (alfacacidol) and phosphate supplements to correct or improve the hypophosphatemia, bowing legs, rickets, and rate of growth in children and improve hypophosphatemia, decrease bone pain, bone deformity and decrease the risk of pseudo-fractures and non-union [16, 42] and periodontitis [43] in adults. Phosphate correction should go in line with vitamin D correction; otherwise, there is the possibility of developing hyperparathyroidism and renal complications [42, 44]. Continuous phosphate supplementation is accompanied by decreased patient compliance due to the requirement of frequent

daily doses of phosphate tablets because its intake is associated with a rapid rise and rapid drop of phosphate in the serum. Another factor that makes the patient not adhere to the treatment is its complication and side effects [44].

Conventional phosphate and active vitamin D3 therapies are associated with improvement in bone deformity, rickets and osteomalacia, growth rate [42], and dental abscesses [44]. Still, the improvement in the growth rate is insufficient; on the other hand, growth hormone therapy would increase the growth rate but could be associated with further bone complications and increased risk of deformities [45]. Early start of conventional treatment as early as one year of age is correlated to better outcomes than after one year of age [46]. However, even in those with an early start of treatment, there is short stature compared to normal children [47]. Little data exist on using these medications in adult patients, but improvement of enthesopathy, osteomalacia, osteoarthritis, and prevention of pseudo-fracture were reported [42].

Advanced therapy

The primary pathophysiology of this disease is an increase in FGF23, which can recently be targeted by using human monoclonal antibodies to treat hypophosphatemia and its associated complications. It was approved and used in 2018 by the FDA for children and adults [42]. This treatment is superior to a mixture of phosphate and alfacalcidol treatment. In addition, it can decrease the FGF23 that is increased in these patients and will result in an improvement in phosphate level and its associated complications [42].

According to the recommendations and guidelines of 2019 on the management of XLH, the use of monoclonal antibodies is required in any patient with XLH who did not benefit from conventional therapy radiologically; bone diseases do not improve, and complications developed with the use of phosphate and active vitamin D medications as conventional therapy, and for non-compliance patient with these medications [44]. In addition, the use of monoclonal antibodies, such as burosumab, is associated with improvement in the growth rate and decreases the risk of development of reduced height. Furthermore, studies investigating the impact of burosumab on pain, fracture healing and overall life quality show promising results [48]. However, despite its effectiveness, its treatment is safe in a double-blind study with six months continuation period treatment in adulthood with XLH [49] and other studies in adults and children. Still, long-term burosumab use needs to be studied, which is required [48].

As hypophosphatemia is associated with bone, dental, and hearing problems, several specialists must manage this condition. The team should include pediatricians specialized in endocrine diseases (if diagnosed from childhood), adult endocrinologists, orthopedics, rheumatologists and even odonatologists, otologists, physical therapists, and psychologists [42]. A large number of patients required operations to correct the abnormality in the legs or other bones, especially in severe limb deformities; the corrective osteotomy is needed, although these operations better to be done in adulthood because before adulthood, it is associated with the risk of reoccurring of the same abnormalities that are why better to be done only in a patient with severe limitation of movement and misalignment, and after epiphyseal closure [50] and according to the recommendation/guideline of 2019, these orthopedic surgeries shouldn't be started if the children on the treatment of less than a year [44].

Dental problems that present from childhood continue to adulthood, and most of the patients lose many teeth when reaching adulthood and could require a denture at an early age [42]. The role of psychologists is also essential, especially in some cases of depression due to the effect of the disease burden and abnormal shape of the legs, abnormal gait, and short stature on self-esteem and social interaction. Even the loss of teeth and bad oral hygiene are among the factor that affects the patient psychologically [42]. Thus, the management should not compromise on medication only, but patient care and follow-up are critical, with psychological support. Most of these patients couldn't socially interact with people and go out or get jobs and continue to work as usual people due to the pain and disability that they have, and due to short stature and other disease complication that affect their psychological health [51, 52]. Thus, an early diagnosis from the beginning of the disease is crucial to decrease the physical, social, economic, and psychological risk and other disease burdens of XLH on the patient [42, 51, 52].

PTH (to avoid secondary hyperparathyroidism) and ALP (to ensure bone healing) should be investigated during follow-up [16]. In addition, radiological monitoring for skeletal deformity/osteopenia and ultrasound (US) to investigate urinary stone formation are also necessary [53].

Therefore, this report aimed to present a case of hypophosphatemia, XLH, with clinical features of the disease from childhood, without seeking medical care for his condition with his mother and his two brothers, who have short statures, bone pain and frequent fractures.

Case presentation

A 27-year old male with disproportionate short stature complained of bilateral lower limb pain and difficulty walking around for a month. An orthopedic physician referred him to the Endocrine Unit of the Internal Medicine in early 2021. A thorough history was taken related to his condition, sociodemographic status, family history, medical history (during childhood and adulthood), surgical history, and drug/medication history.

Baseline biochemical profiles of the studied patient are given in the Supplementary **Table**.

His condition started with paresthesia in both lower limbs in the last six months, progressing gradually with pain in both thighs and shins. The pain was mild, and then the pain and paranesthesia became severe over time. After one month, he started to have nodular swelling and pain in both thighs and shins. The pain was more on the left lower limb affecting his daily activity. Progressively over a month, he became disabled and could not move around without help.

Ethical approval

All procedures in this study were performed following the ethical standards of the national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. On the other hand, written informed consent was taken from the patient to publish his data and images. The research was

approved by the scientific and ethical committee of the College of Medicine, the University of X, meeting No. 4 on October 05, 2021.

Childhood and past medical histories

In the narration of the patient's mother and brother, he was born generally at full term. During his childhood, he was unlike his peers as his walking was slower, and his height was shorter even after puberty. In addition, he had a history of recurrent falls, and he could not do exercise; despite the problems mentioned above, they did not seek medical help previously, only one time because of the detection of bowing of his leg; they brought him to a surgeon who recommended and asked for operation, but they could not agree to do the process, because of the high cost and their financial situations, and did not visit hospital or clinic for follow up visits later on. He did not assess for rickets and did not receive active vitamin D3. His dentition was delayed to 2–3 years of age. He also complained of paresthesia, inability to walk efficiently, and the development of muscle pain after a long walk that prevents him from sleeping at night. He did not have known hematological problems, anemia or treatment for these conditions.

He did not have a hearing problem; however, he had a history of otitis media at age 21 years and received treatment and improved. Also, he had tooth and gum problems, with toothache throughout his life, which made him extract several teeth because of loosening his teeth due to gum inflammation, and he could not eat hard food; his dentist stated that he could not do an implant because of his weak gum. He did not have a history of cardiovascular, respiratory, gastrointestinal, or genitourinary systems problems with no history of renal stone or dysuria.

Family history and family member

He had two brothers and one sister; his father was healthy and died in an accident without any health problems. On the other hand, his mother and brothers (older than him) had short stature from childhood and skeletal abnormalities. Still, they did not visit the hospital; only his brother visited the hospital after acute pain in the left thigh with the inability to walk, which was diagnosed with a stress fracture fixation of his fracture was made with a surgical operation. Still, the cause of his stress fracture did not find as he refused to be investigated and examined for his condition. At the same time, his married sister had minor thalassemia; otherwise, she was healthy and had two healthy children with average heights. His uncles and aunts were healthy; three of his uncles died as elderly due to chronic diseases without apparent skeletal abnormalities. His cousins were healthy without short stature, but none of his uncles, aunts, or cousins' height exceeded 160 cm.

Socioeconomic state

The patient was from a low-income family that lived in a rural area. His father died a long time ago. Nevertheless, he studied and passed school successfully and graduated from the College of Agriculture, in 2016. After his graduation and because of unemployment, he started working and standing for about nine hours each day, selling popcorn and French fries on carts outdoors with his brother till his situation became worse and he developed severe pain in his lower limbs and disability.

Medication and drug history

He did not use a known drug, and there was no history of chronic medication use; he was not a drug user, smoker, or alcohol drinker.

General clinical examination and workup for the patient

The patient's vital signs were typical, with a pulse rate of 81 beats/minute (bpm) and arterial blood pressure of 105/70 mm Hg. Anthropometric parameters were measured, including height (145 cm), weight (52 kg), and BMI (24.73 kg/m^2). On systemic examination, there was no pallor, jaundice, cyanosis, or leg oedema. Cardiovascular and pulmonary tests were routine. Musculoskeletal investigation revealed; short stature with a short forearm and bowing of the legs. He had bilateral thigh nodular mass and tenderness in which the nodular swelling of the thigh was more on the left side. His grade of POWER was G4. Hematological and biochemical analyses for serum and urine were done.

Orthopedic examination

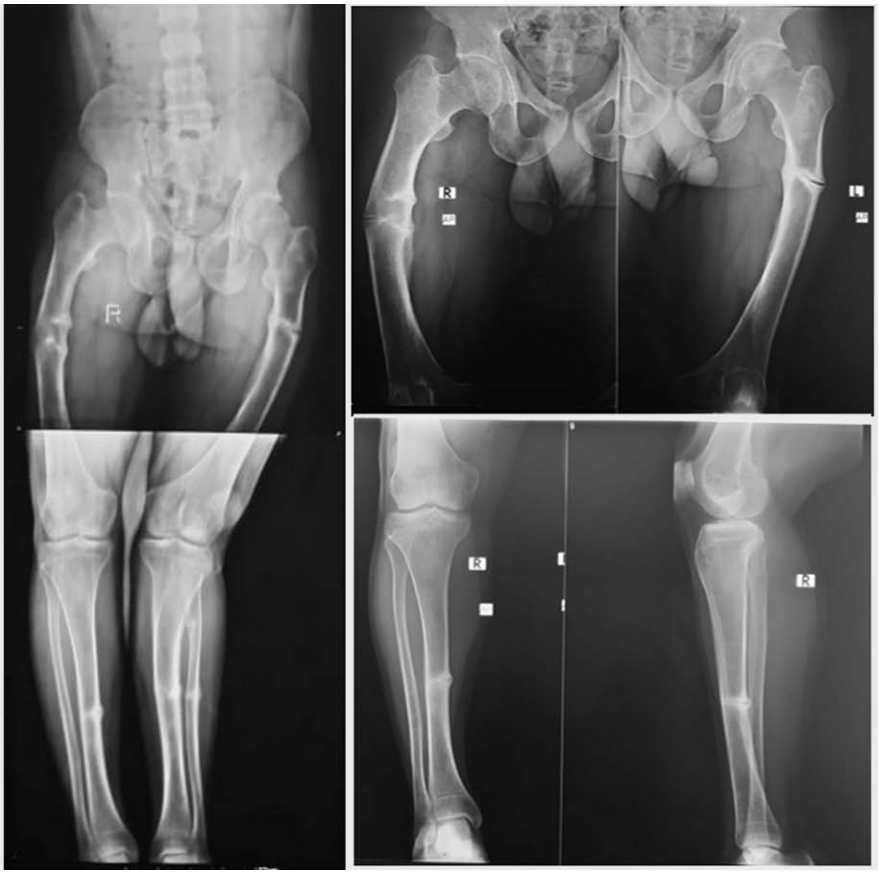
He had a waddling gate, deformity with signs of stress fracture and union of both upper and lower extremities on radiograph and physical examination with coronal deformity. There was no hypotonia with normal reflexes and range of motion of all joints in the upper and lower extremities. Bilateral bowing of both femurs with a normal range of motion in both hips and knee joints was also observed. The left knee was valgus about 20 ° while the right knee was varus about 12 ° (▶ **Fig. 1**). Also, he had a windswept deformity, which supports the metabolic cause of dwarfism. There was no pain/tenderness in the chest with no signs of fracture or united fractures. Examination of the oral cavity, showing poor oral hygiene, dental carries, missing of several teeth, gingivitis, and de-papillated tongue (▶ **Fig. 2**)

Radiological assessment

After history and clinical examinations, a radiological investigation and DEXA scan were performed. The patient was sent for the AP and lateral view plain radiographs of both upper and lower limbs, wrist/hands, PA view chest radiograph and lateral view plain radiograph of the lumbosacral region. There was generalized diffuse osteopenia of the skeleton, with thinning of the cortex and loss of bone marrow trabeculation, varus deformity of right femur about 25 °, looser zone of both mid-shaft femur and mid-shaft tibia, which indicates stress fracture of compression part of a long bone (▶ **Fig. 1**). Chest radiograph was normal, with no signs of stress fracture or the looser zone in the ribs, with regular thoracic cage and lumbosacral spines, and average wrist and hand plain radiograph, no more open area in the upper limbs, but there was bowing of both humerus with signs of previous fractures in both humerus and right radius (▶ **Fig. 3**). DEXA scan showed severe osteoporosis with an average trabecular bone score (TBS). Bone mineral density (BMD) at the left femur neck was 0.636 g/cm^2 with a markedly low T-score (–3.0) and a Z-core of –2.5.

Biochemical investigations

At baseline, his renal/liver function tests, serum electrolytes, and lipid profile were average except for low high-density lipoprotein



▶ **Fig. 1** Plain radiograph (scanogram) of pelvis, both hips, both knees, and both ankle joints in AP standing. The AP and lateral view of the right leg are shown at the bottom right of the figure. This plain radiograph shows generalized diffuse osteopenia, with thinning of the cortex and loss of bone marrow trabeculation, looser zone and stress fracture in both mid shaft femur and tibia, Bilateral femora vara, genu varum of the right knee, and genu valgus of the left knee.

(HDL). Complete blood count (CBC) showed raised red blood cells (RBC) count with low hemoglobin (Hb) and packed cell volume (PCV). Blood film showed microcytic hypochromic anemia with completely normal iron status. Hb electrophoresis was recommended to exclude thalassemia minor for his hematological abnormality. Tissue transglutaminase antibodies IgG and IgA were also normal.

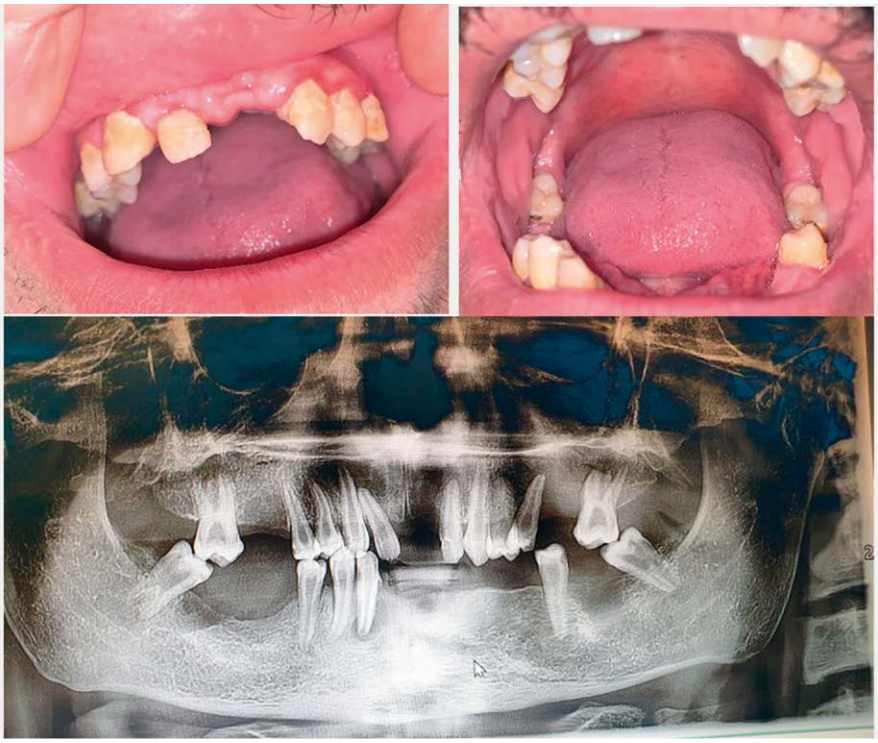
On the other hand, his assessment of bone status showed decreased serum phosphate with low 25-vitamin D3 and slightly elevated PTH and considerably raised ALP with normal serum calcium (▶ **Table 1**). Renal tubular acidosis was excluded, with an average serum bicarbonate level and no glucosuria. The 24-hour urine collection was investigated but gave false results due to inadequate urine collection because of his pain, deformity, and inability to collect urine appropriately. Urine phosphate, calcium, and creatinine were assessed from a single sample of urine (R: Medscape) and showed elevated urine phosphate levels. At the same time, with the assessment of serum phosphate and creatinine, the fractional excretion rate of phosphate (FEP_{Pi}) and renal tubular reabsorption of phosphate (TRP) was calculated. F_{PE} was 0.803, while TRP was lowered to 19.7 %. Thus, the computed maximum tubular reabsorption of phosphate per glomerular filtration rate (MTP/GFR) was 1.69.

Therefore, based on these investigations, a diagnosis of hypophosphatemia was made, and the treatment was started with phosphate (1.0 g/day) and alfacalcidol (1.0 µg/day). In addition, his whole blood sample was sent for PHEX and FGF23 gene sequencing.

Follow-up

All follow-up examinations were recorded, and the improvement/any change in his investigation or clinical condition was recorded. Two months later, he visited the hospital to follow up, and his clinical status was greatly improved; he walked without any walking aid, slightly limping, with no pain in the bone of the lower limbs. The biochemical investigation for the bone status and CBC have performed again; there was an improvement of his serum phosphate level toward normal, with an increase in his PCV and Hb, while there was an increase in his RBC farther from normal.

In the whole sequencing for PHEX and FGF23 genes, a pathogenic variant was detected for the PHEX gene with X-linked dominant inheritance. At the same time, no pathogenic variant was detected for the FGF23 gene. Genetic testing for his mother and brothers were recommended, but they were living in a rural area and had not agreed to visit the hospital at city center to conduct the test. Based on these investigations, the diagnosis of XLH was



▶ **Fig. 2** Picture of the oral cavity with X-ray imaging showing poor oral hygiene, dental caries, missing several teeth, gingivitis, and de-papillated tongue.

▶ **Table 1** Bone profile assessment at baseline and follow-up visits of the studied patient.

Parameter	Normal Range	Baseline	1st follow-up	2nd follow up	3rd follow up	last follow up
Total serum Ca^{+2} (mg/dl)	8.3–10.8	9.39	8.64	9.81	–	8.58
Free serum Ca^{+2} (mg/dl)	4.61–5.33	–	–	–	4.49	–
Serum phosphate (mg/dl)	2.7–4.5	1.0	2.07	1.6	1.4	2.1
PTH (pg/ml)	15–65	81	–	–	61.55	82.32
25-Hydroxyvitamin D (ng/ml)	30–100	13	–	29.1	12.82	22.13
ALP (IU/l)	46–126	193	–	–	205	278

Ca^{+2}: Calcium; PTH: Parathyroid hormone; ALP: Alkaline phosphatase.; Note: Total serum Ca^{+2} was corrected for albumin.

confirmed. One month later, the phosphate level was slightly decreased again. Thus, the phosphate dose was increased to 2.5 g/day for better improvement.

On patient follow up another month later, although the patient was clinically felt well but the phosphate level began to decrease again to 1.6 mg/dl, with normal serum calcium and increased 25-hydroxyvitamin D3 from 13 to 29.1 ng/ml. Thus, the patient was recommended to continue on the prescribed medications. He addressed that he took his medication regularly upon questioning, and he suggested to be maintained on the same high phosphate dose (2.5 g/day) because of his low serum phosphate level.

The patient could not attend his follow up visits to medical and endocrine follow-up in next month as he underwent a surgical operation in preceding month, to fix left femur shaft fractures with corrective osteotomy. Consequently, his left femur was fixed with locked intramedullary nail which provide prophylactic fixation for the stress fracture, also (▶ **Fig. 4**).

On next follow up visit, the patient came to follow up, then plain radiograph AP and lateral view of both thigh and legs were performed, and there were no signs of the union at the fracture site that could be the result of the failure of intramedullary nail to place correctly due to the deformity. On his plain radiograph, signs of osteopenia and osteoporosis were still existed with thinning of the

cortex and loss of bone trabeculation. He complained of right hip and knee pain due to leg length discrepancy, and next operation was recommended. Examination of the gait revealed limping Trendelenburg type due to leg length discrepancy, with a 2.0 cm discrepancy in the length of the lower limbs upon standing. There was no hypotonia with normal reflex/range of motion of all joints in the upper and lower extremities (▶ **Fig. 4**).

Biochemical investigations showed a greater decrease in phosphate level; although the patient denied that he decreased intake of the phosphate tab, and he did not address any complain about receiving his treatment. While during his next visit and upon further questioning and doubting a further decrease in his phosphate level, he claimed that he got diarrhea when he received an increased dose of phosphate. Thus, he did not take medicine daily rather, he received it irregularly for the last seven months. Therefore, the dose of the phosphate tab was decreased to 1.0 g/day, to reduce the side effects and failure of phosphate reabsorption. Hence, the patient was advised to consult his doctor for any complaint about his medications rather than receiving it haphazardly. The result of Hb electrophoresis revealed beta thalassemia minor (HbA2 of 5.6 % while its normal range is 1.5–3.5 %).

On last follow up, after a month from receiving the phosphate tab, typically with a 1.0 g/day dose, his biochemical situation was better; the phosphate began to elevate toward normal, with increasing 25-hydroxyvitamin D3 and even improvement in the CBC values toward normal with the following improvements: baseline versus final value of 35.5 vs 41.1 % for PCV, 11.7 vs 13.4 g/dl for Hb, with serum phosphate value of 1 vs 2.1 mg/dl (▶ **Table 2**). A week later, the next operation was performed.

Discussion

In this study, we comprehensively studied hereditary hypophosphatemia in a male patient aged 27 years old using various clinical, laboratory, and imaging assessments. However, his family members, including his mother and his brothers supposed to have the same disease but did not agree to visit the hospital to confirm their case using advanced molecular investigation and receive treatment to improve their condition.

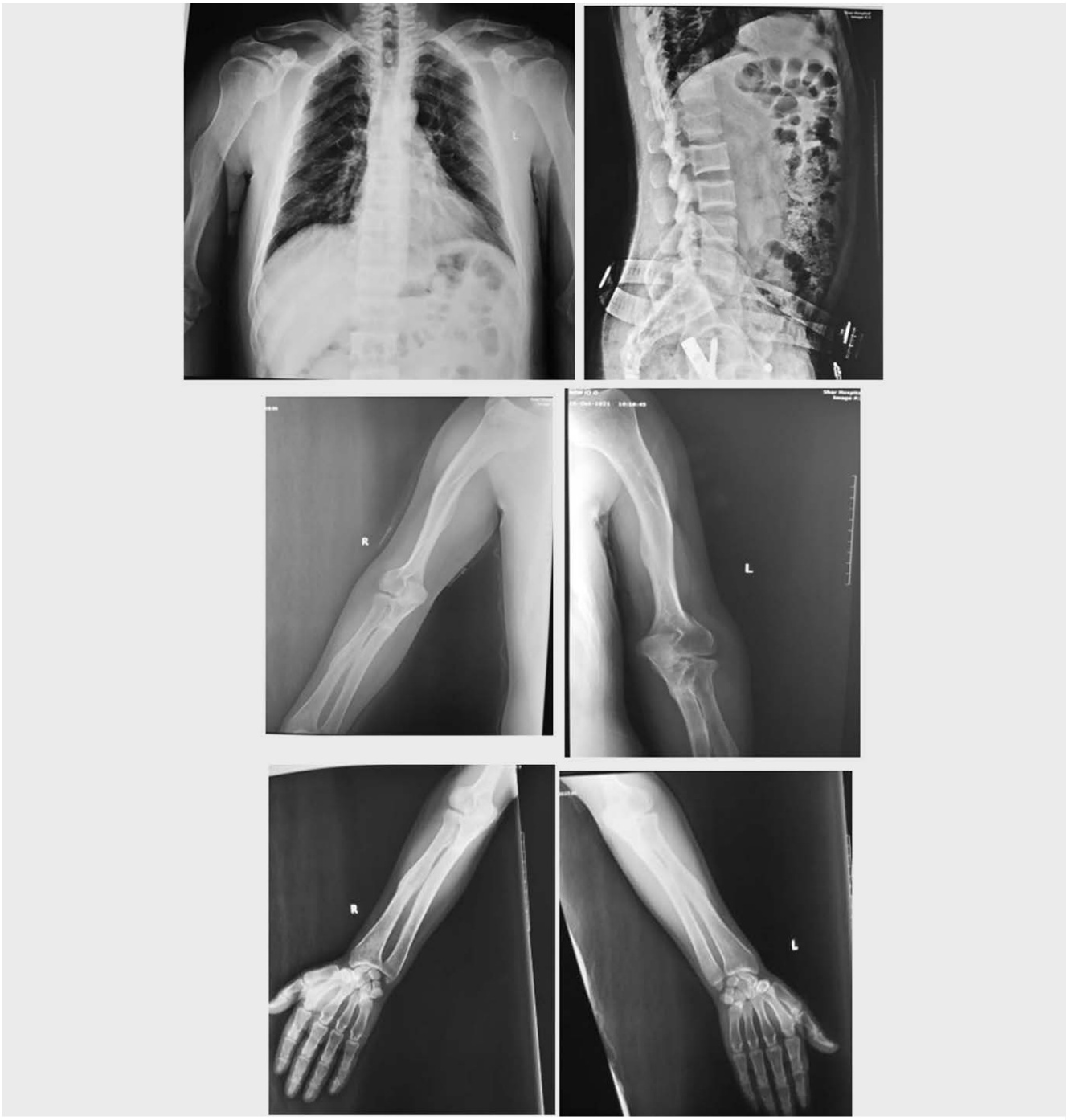
The PHEX gene is expressed in bone, teeth, and parathyroid glands that negatively regulates FGF23 expression through an unknown mechanism. The FGF23 has a phosphaturic effect to maintain circulating phosphate levels within a normal range. Osteocytes and osteoblasts excrete it as the physiological response to hyperphosphatemia. The same effect on the expression of the FGF-23 has elevated 25-hydroxyvitamin D levels in the blood and probably PTH [54]. Thus, FGF-23 is essential in regulating the homeostasis of phosphorus and partially of calcium. Numerous hereditary and acquired diseases occur due to increased or decreased activity of the FGF-23, such as those caused by inactivating mutations in the PHEX gene [55]. Thus, in this study, we confirmed that the patient's hypophosphatemia occurred due to PHEX gene mutation and removal inhibitory effect of the PHEX gene on FGF23 and thus increased loss of phosphate in the urine. The same outcome was found in other case reports studies such as Bacchetta and Salusky, 2012 [2], Radlović et al., 2014 [54], and Rafaelsen et al., 2015 [25].

We have realized that the patient's bone and joint irregularities and deformities that made him use a walking aid resulted from prolonged hypophosphatemia that was not diagnosed during his childhood and not receiving a specific treatment to correct his case to some degree or prevent further sequelae. Furthermore, since it is known that the maintenance of the levels of intra and extracellular phosphate inside a narrow band is essential for several biological processes, including energy metabolism, skeletal development and bone integrity besides, phosphorus deficiency can compromise chondrocyte maintenance, causing the block of bone formation, resulting in delayed growth and rickets, therefore justifying the short stature and other skeletal deformities in the reported patient [56].

The whole follow-up period for this patient was one year. Although some skeletal abnormalities were already developed and could not be corrected, using phosphate tablets in this patient improved his pain and physical activity significantly from a disabled patient to a patient that could walk on his own with a walking aid (stick) only. Most clinical signs related to hypophosphatemia were significantly improved, including painful bones and joints, especially on the lower extremities, inability to walk correctly, and improvement of his serum biochemical parameters and hematological tests, especially phosphate level, were found. The same findings were seen in other case studies such as Maia et al. 2018 [57]; Sarat et al. 2016 [58]; and Radlović et al., 2014 [54]. The medications (phosphate and active vitamin D supplementations) also improved his PCV and Hb. Better phosphate control was associated with better PCV and Hb level in this patient, as revealed through 12 months of follow up. This improvement in PCV and Hb could be explained by lowering of FGF23 toward normal level after phosphate supplementation. To our knowledge, no previous studies linked the improvement of PCV/Hb with phosphate level correction, phosphate, or active vitamin D supplementation in familial hypophosphatemia, or in thalassemia patients, this requires thorough study especially in thalassemia patients. Recent study in The Netherlands, demonstrated an evidence of erythropoietin-FGF23 signaling pathway in bone marrow progenitor cells and its relation to hereditary anemia [59]. Collectively, the medication improved his laboratory results to approach normal levels and cleared profound clinical signs that deteriorated his health condition for an extended period. Some of his skeletal deformity was also corrected with an operation and corrective osteotomy for bowing the femur. However, his osteopenia and osteoporosis could need longer periods of phosphate use to be revealed, and the other bone deformities could require more than one surgical operation.

Conclusions

In conclusion, we realized that awareness among physicians is needed upon presenting a case to them with collective clinical signs of rickets/osteomalacia, stress fracture, poor dentition, etc. to medical professionals. Further questioning regarding other systems, receiving detailed history, physical examination and follow-up could identify a case of hypophosphatemia. Most complications and deformities could be preventable, especially if diagnosed early in childhood. Besides, sending samples for genetic confirmation is a gold standard to confirm the diagnosis of hered-



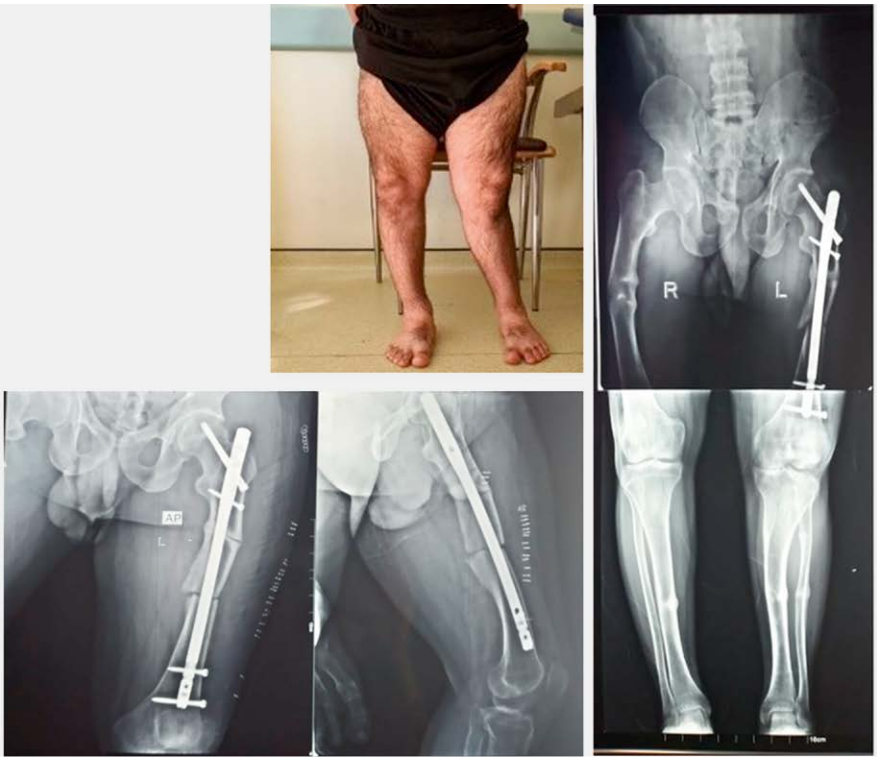
▶ **Fig. 3** Plain radiograph of (**a**) chest (PA view) and lumbosacral spine (lateral view) reveals normal Thoracic cage, no signs of union or looser zone in the ribs, (**b**) Upper extremities shows osteopenia and bowing of both humerus and signs of previous fracture in both humerus, and right radius, with no looser zone.

itary hypophosphatemia. Thus, to prevent patient disability and patient and family burden, which will also cause a burden on the community, it is essential to diagnose and treat this condition early. At the same time, the health system must spread awareness among community members to seek medical health before and not ignore a situation like this if they have, and continuous patient compliance to the follow-up and adherence to their medications is essential. The earlier the treatment and patient compliance, the better patient outcome, associated with fewer burdens on the community. Using phosphate tablets, even in adulthood, could improve some disabilities and prevent further fractures, deformities, and disease sequelae. Better adjustment of phosphate dose is crucial. Although a high phosphate dose could be required, it might be associated with higher complication, diarrhea, and less patient compliance with poorer phosphate control. Further study is needed to find the association of phosphate supplements doses and serum phosphate

▶ **Table 2** Hematological, CBC, and iron status investigations of the studied patient.

Parameter	Normal range	Baseline	1st follow up	3rd follow up	last follow up
WBC	$4.0–11\times10^9$/l	5.6×10^9	7.3×10^9	7.6×10^9	7.3×10^9
RBC	$4.5–5.5\times10^{12}$/l	5.7×10^{12}	6.37×10^{12}	6.18×10^{12}	6.45×10^{12}
PCV (%)	35–55	35.5	40.9	38.8	41.6
Hb (g/dl)	11.5–16.5	11.7	–	12.3	13.4
MCV (fl)	75–100	62.3	–	62.8	64.5
MCH (pg)	25–35	20.6	–	20	20.8
MCHC (g/dl)	31–38	33	–	31.8	32.2
RDW (%)	10–14	14.4	–	15.5	15.3
Platelet	$150–450\times10^9$/l	319×10^9	335×10^9	336×10^9	309×10^9
Ferritin (ng/ml)	30–400	282.2	–	201.2	–
Transferrin (mg/dl)	200–360	–	–	251	–
Total Iron (µg/dl)	65–175	–	–	119	–
TIBC (µg/dl)	250–410	–	–	291	–

CBC: Complete blood count; WBC: White blood cell; RBC: Red blood cell; PCV: Packed cell volume; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; TIBC: Total iron binding capacity.



▶ **Fig. 4** These images show post-operative examination and imaging, in the top left image, the patient standing with 2 cm discrepancy in the length of the lower limbs. Corrective osteotomy for the left femur with locked intramedullary nails, which provided prophylactic fixation for the stress fracture also. Plain radiographs show non-union four months after the operation.

with hematological values, especially PCV and Hb in healthy individuals, and patients with hypophosphatemia with or without hereditary anemia.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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