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Case Report

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A Rare Case of Pediatric X-Linked Hypophosphatemic Rickets: Challenges and Insights from Pakistan

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Abstract

Introduction and Importance: X-linked hypophosphatemic rickets (XLHR) is a rare hereditary disorder characterized by impaired phosphate metabolism, leading to skeletal deformities and growth retardation. XLHR prevalence rates vary globally, with limited data from Pakistan. This case report presents a 14-month-old boy from Pakistan with XLHR, detailing the clinical presentation, diagnostic approach, and management.

Case Presentation: The individual displayed common symptoms of XLHR, such as stunted growth, limb abnormalities, and biochemical irregularities. Radiographic assessments confirmed skeletal alterations typical of XLHR. Treatment involved phosphate supplementation alone, as active vitamin D analogs were avoided due to prior vitamin D injections resulting in intoxication. Close monitoring and follow-up were implemented.

Clinical Discussion: This case highlights the clinical features and management of XLHR in a Pakistani pediatric patient. Early recognition with radiographic imaging is crucial to identify distinct skeletal abnormalities and biochemical tests showing elevated alkaline phosphatase (ALP) and renal phosphate wasting. Molecular genetic testing confirms the diagnosis by detecting PHEX mutations. Management typically includes oral phosphate supplements and active vitamin D analogues varying on the case to counteract excess fibroblast growth factor 23 (FGF23) and Burosumab, a novel therapy targeting FGF23. Despite optimal medical management, some patients may require surgical correction for worsening skeletal deformities, with methods ranging from growth modulation techniques to more invasive procedures like osteotomies and fixation.

Conclusion: This case highlights the challenges of recognising and reporting rare genetic disorders like X-linked hypophosphatemic rickets (XLHR) in Pakistan due to limited data and awareness. Improved access to genetic testing and increased awareness among healthcare professionals is crucial for better management and support for affected individuals and families, ultimately improving outcomes and quality of life.

Keywords: X-linked hypophosphatemic rickets; Skeletal Abnormality; Paediatric

Introduction

Rickets, a childhood bone disorder, is marked by bone softening and weakening due to insufficient vitamin D, calcium, or phosphate [1]. The etymology of the term "rickets" remains somewhat ambiguous in medical literature. Nevertheless, it is speculated to derive from the German term

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"wricken," which conveys the meaning of "twisted" [2,3]. Typically associated with nutritional deficiencies—specifically, lack of vitamin D and calcium, known as nutritional rickets—this form is manageable through dietary adjustments and sun exposure, aiding vitamin D synthesis in the skin [4]. In contrast, genetic rickets, exemplified by X-linked hypophosphatemic rickets (XLHR), result from inherited mutations disrupting phosphate metabolism, causing hypophosphatemia independently of vitamin D levels. XLHR, the predominant hereditary form, stems from PHEX gene mutations on the X chromosome, governing phosphate regulation and bone mineralization. Unlike nutritional rickets, managing XLHR involves intricate pharmacological interventions to correct phosphate levels and vigilant monitoring of bone health [5,6].

Presentation of Case

A 14-month-old boy was brought in by his parents to the pediatric clinic due to concerns regarding his general health and limb deformities, along with growth delay. When inquired about family history, consanguinity was noted in the family and a similar case of his cousin was diagnosed with XLHR. The patient is the only child of his parents. Before his current presentation, he had been receiving vitamin D supplementation and multivitamins. Despite these treatments, he exhibited difficulties walking and leg bowing.

Physical examination indicated growth retardation, with measurements of height, weight, and head circumference all falling below the 5th percentile. Clinical manifestations included leg bowing, wrist widening, proptosis, bulging eyes, abdominal distension, and a smaller-than-normal chest (Figure 1). His walking pattern appeared waddling, and his stature seemed noticeably shorter than expected for his age. Upon initial examination, typical signs of rachitic deformities were observed, primarily affecting the bones of his lower extremities, resulting in coxa vara and genu varum.

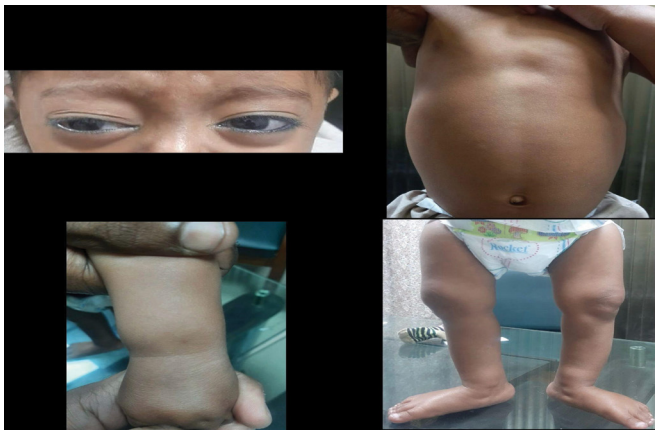

Figure 1: Clinical Picture of the Patient Showing Manifestations Including Proptosis, Bulging Eyes, Abdominal Distension, a Smaller-than-Normal Chest, Wrist Widening, and Leg Bowing.

Following a thorough evaluation, laboratory tests revealed anomalies in his serum phosphate levels, raising suspicion of a metabolic bone disorder. Laboratory assessments demonstrated low serum phosphate levels (3.5 mg/dL) and significantly elevated alkaline phosphatase (ALP) levels (2032 IU/L). His 25(OH) vitamin D level was elevated (107.8 ng/mL), indicative of vitamin D intoxication. Imaging studies showed diminished bone density, along with metaphyseal abnormalities, on X-rays. Given these findings, his age, and his positive family history, X-linked hypophosphatemic rickets (XLHR) was considered as a potential diagnosis. Genetic testing was not available in our country.

Following the diagnosis, the treatment commenced promptly, involving phosphate supplements and without any active vitamin D analogues to rectify phosphate wasting and stimulate bone mineralization. Education about the condition and the importance of treatment adherence were provided to the boy's parents. Regular follow-up appointments were scheduled to closely monitor his progress and make any necessary adjustments to the treatment plan, aiming to optimize his outcomes despite the challenges posed by XLH. Additionally, it was noted that prior to this diagnosis, vitamin D had been administered in injection form under the assumption that the boy was suffering from conventional rickets. However, this approach failed to produce any improvement, and subsequent laboratory tests indicated that this method had actually led to vitamin D intoxication, highlighting the necessity for the precise diagnosis and tailored treatment approach now being followed. Treatment and management strategies included initiating phosphate supplementation, without any active vitamin D (calcitriol) to address phosphate wasting and encourage bone mineralization (Figure 2). Close monitoring of his serum phosphate, calcium, parathyroid hormone (PTH), alkaline phosphatase (ALP), and vitamin D levels was essential to evaluate treatment response and guide adjustments. Ongoing management aimed to optimize

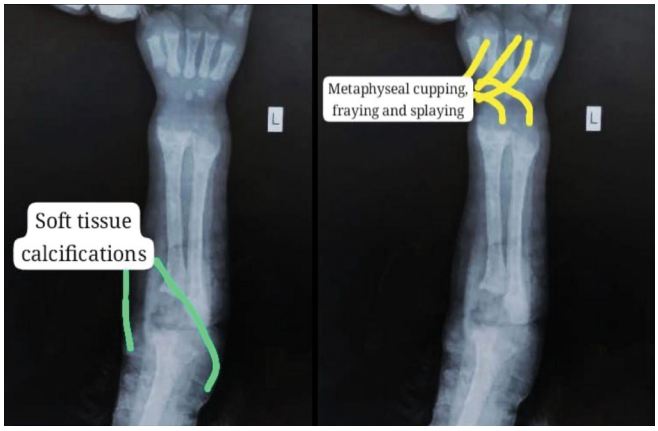

Figure 2: X-ray of the patient's left arm displaying soft tissue calcifications attributed to excessive vitamin D intake on the left, alongside metaphyseal cupping, fraying, and splaying on the right side.

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the boy's bone health and overall development, with his condition and response to treatment informing subsequent interventions.

Discussion

Reported prevalence rates between 1 in 20,000 and 1 in 200,000 [7,8]. We are detailing the third case from Pakistan, employing a comprehensive approach that integrates clinical symptoms, radiological findings, and laboratory reports. Persistent hypophosphatemia in X-linked hypophosphatemia (XLH) results in compromised endochondral mineralization within the growth plates of long bones, leading to structural deformities. Among children and adolescents with XLH, there is a notable impact on growth, accompanied by myopathy, bone pain, and dental abscesses [9]. XLH stands as the predominant hereditary contributor to phosphopenic rickets/osteomalacia. Additionally, hypophosphatemia is observed in calcipenic rickets/osteomalacia, primarily attributed to secondary hyperparathyroidism [10].

X-linked hypophosphatemia (XLH) typically manifests within the first two years with symptoms such as leg bowing, impaired growth, bone tenderness, muscle weakness, dental problems, increased fracture risk, widened wrists, hearing loss, and kidney stones, attributed to low phosphate levels. Skeletal abnormalities like bowed legs, knock knees, and frontal bossing affect mobility, while joint pain, often the initial complaint, results from hypophosphatemia's impact on joint cartilage. Dental complications, including abscesses, delayed tooth eruption, and enamel defects, are common, along with neurosurgical conditions like craniosynostosis and Chiari 1 malformations. Accurate diagnosis and management are crucial due to the varied clinical presentations, which may also include non-skeletal issues such as sacroiliitis [11-14].

Radiographic imaging serves as the initial diagnostic step for XLH, often preceding biochemical tests, with diagnosis indicated by distinct radiographic findings and confirmed through elevated alkaline phosphatase (ALP) and renal phosphate wasting. Molecular investigation further verifies the diagnosis by identifying PHEX mutations. In XLH and other rickets forms, the growth plate (physis) exhibits a unique radiographic appearance marked by increased height and widening due to impaired endochondral ossification. Normal physis maintains a layered structure with resting, proliferative, and hypertrophic zones, but in rickets, widened physis results from the absence of mature hypertrophic chondrocyte apoptosis. Mineralization deficiency is notably observed at metaphyseal zones, leading to excess non-mineralized osteoid, growth plate widening, and abnormal metaphyseal features like fraying, splaying, cupping, and Looser's zones (pseudofractures) on the compression side of bones, especially pronounced in rapidly growing areas like the distal femur, proximal tibia, ulna, and forming the rachitic rosary at the anterior rib ends [15]. XLH diagnosis relies on identifying distinct clinical, biochemical, and radiographic features, confirmed by molecular genetic testing detecting a hemizygous PHEX pathogenic variant in males or a heterozygous PHEX pathogenic variant in females [16].

Medical management of X-linked hypophosphatemia (XLH) focuses on addressing underlying mechanisms and symptoms, typically involving oral phosphate supplements and active vitamin D analogues to counteract excess fibroblast growth factor 23 (FGF23). Dosages vary depending on individual needs, typically ranging from 20 to 60 mg/kg/day for phosphate and 1 to 3 µg/day for alfacalcidol or 0.2 to 1.5 µg/day for calcitriol. Due to constant renal phosphate wasting, multiple daily phosphate doses may be necessary, often starting at low levels and gradually increased to minimize gastrointestinal side effects. Higher doses are often required during periods of rapid growth, such as infancy and puberty [17,18].

Burosumab, a novel therapeutic approach for X-linked hypophosphatemia (XLH), targets FGF23, enhancing phosphate reabsorption and normalizing serum phosphate levels by restoring renal sodium-phosphate cotransporter function. Clinical studies in pediatric patients have demonstrated its effectiveness and safety, leading to regulatory approval for market availability. Burosumab is generally well-tolerated, with injection site reactions being the predominant side effect observed in trials. Other reported adverse events, such as headache, vomiting, and decreased vitamin D levels, were considered unrelated to the drug by investigators. Notably, no evidence of hyperphosphatemia or ectopic mineralization was observed [19-21].

Despite optimal medical management, 25–65% of XLH patients may still need surgical correction for worsening lower limb deformities. Minimally invasive methods like hemiepiphysiodesis with eight plates are common for growth modulation, while severe cases may require osteotomies and fixation. Burosumab shows promise in improving leg deformities, but its role in preventing complications and surgery needs more study. Successful orthopedic surgery in XLH patients relies on effective medical treatment, precise planning, and various correction methods tailored to each case [21].

Conclusion

This case sheds light on X-linked hypophosphatemic rickets (XLHR) in a pediatric patient from Pakistan, highlighting the challenges of under-recognition and under-reporting of rare genetic disorders in this region. Despite global prevalence estimates, limited data exist on XLHR in Pakistan, underscoring the need for increased awareness, diagnostic vigilance, and comprehensive management

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strategies. Efforts to improve access to genetic testing are essential to address the under-reporting of XLHR and other rare diseases in Pakistan. By enhancing awareness and understanding of XLHR and its management, healthcare professionals can better support affected individuals and families, ultimately improving outcomes and quality of life in this population.

Declarations

Consent for publication: Written informed consent was obtained from the patient's parents for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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