APMB - Atti della Accademia Peloritana dei Pericolanti
Classe di Scienze Medico Biologiche
Vol. 112(1) 2024

ISSN 1828-6550

DOI: 10.13129 / 1828-6550 / APMB.112.1. 2024.CCS4

Clinical case Seminar

CCS 4 (1-7)1-5)

The importance of early diagnosis of X-linked hypophosphatemic rickets: a case report.

Francesca Franchina, Fabio Toscano, Giovanni Luppino, Giorgia Pepe, Tommaso Aversa, Domenico Corica.

Department of Human Pathology of Adulthood and Childhood, Unit of Pediatrics, University of Messina, Messina, Italy.

Abstract

X-linked hypophosphatemic rickets (XLH) is the commonest inherited form of rickets. XLH is caused by an impaired regulation of fibroblast growth factor 23 (FGF23) due to a PHEX gene mutation, leading to chronic renal phosphate excretion and impairment of vitamin D activation. Children with XLH show clinical signs of rickets, short stature, stunted growth, deformities of the lower limbs, bone and muscular pain, weakness and reduced quality of life.
XLH is a multisystem disease that requires a multidisciplinary approach, as patients may experience hearing loss, progressive bone deformities, recurrent dental and periodontal lesions. Burosumab, a fully human IgG1 monoclonal antibody to FGF23, represents the emerging gold standard treatment for XLH, whose effect appears to be significantly better clinically, biochemically and radiographically than conventional therapy. Early initiation of specific therapy improves the bone outcome of these individuals.
This report describes an emblematic case of an 11-year-old girl with lower limb varus and short stature in whom the diagnosis of XLH was made late. This case highlights the importance of including the evaluation and correct interpretation of calcium-phosphorus metabolism in the diagnostic work-up of short stature, with the aim of diagnosing cases of XLH at an early stage, initiating the most appropriate therapy, and avoiding surgical treatment if possible.

Key-Words: X-linked hypophosphatemic rickets; burosumab; short stature

Introducing Member: Domenico Corica

Corresponding Author: Francesca Franchina, francesca.franchina8@gmail.com

Introduction

Rickets is a skeletal abnormality resulting from impaired apoptosis of hypertrophic chondrocytes and delayed mineralization of growth plate cartilage (1). Rickets can occur as a consequence of vitamin D deficiency or, more rarely, of abnormality in the vitamin D receptor or a phosphate deficiency (2).
X-linked hypophosphataemic rickets (XLH) is the most common cause of inherited rickets, with a prevalence of 1:20,000-60,000 (3; 4). XLH is an X-linked dominant disorder caused by mutations in *PHEX* gene, which encodes a phosphate-regulating neutral endopeptidase PHEX, predominantly expressed in osteoblasts, osteocytes and teeth (5). The loss-of-function mutations of PHEX result in enhanced secretion of the phosphaturic hormone called fibroblast growth factor 23 (FGF23) and increased renal 24-hydroxylase activity. These factors affect renal phosphate wasting causing hypophosphatasemia and diminished synthesis of active vitamin D (calcitriol). Therefore, the characteristic biochemical pattern consists of hypophosphatemia associated with renal phosphate

wasting, low serum levels of calcitriol, normal serum levels of calcium, parathyroid hormone and 25-hydroxyvitamin D.

The clinical picture is characterized by clinical signs of rickets, lower limb deformities, disproportionate short stature, weakness, delayed motor development and delayed walking, pain and poor mineralization of teeth (4). These clinical manifestations usually occur during the first or second year of life, although they vary from mild to severe systemic involvement (4). In the diagnostic assessment of XLH, radiographic evaluation is crucial in order to assess the degree of bone involvement with the rickets severity score (RSS). The RSS will be estimated by assessing the degree of involvement of metaphyseal fraying, concavity, and the proportion of the growth plate at the wrists and knees (6).

Conventional therapy, consisting in multiple daily doses of active vitamin D metabolites and oral inorganic phosphate salts, frequently does not significantly improve phosphate metabolism and it shows poor and slow effects in improving rickets lesions and linear growth. Conventional therapy is also burdened by poor adherence to treatment, especially in children and adolescents, mainly due to the several daily doses of drugs (up to six per day) and the side effects mainly related to phosphate salts (e.g. gastointestinal symptoms). Conventional therapy is also difficult for physicians to manage as it is necessary to balance the benefits of treatment and the potential risks of overtreatment that could lead to hyperparathyroidism, hypercalciuria, nephrocalcinosis, and nephrolithiasis (4; 7).

Better understanding of the pathophysiology has recently led to the development of a target-drug, Burosumab, a recombinant human IgG1 monoclonal antibody against FGF23, indicated for the treatment of XLH, from the age of one year, in the presence of bone damage assessed by the RSS (RSS >1.5) (8).

Recent studies documented that Burosumab results in significant improvements in serum phosphate concentration and tubular phosphate reabsorption, associated with rapid recovery of radiological signs of rickets, a reduction in osteoarticular and muscular pain and improvement in physical function in patients with XLH RSS >1.5 (9; 10). During the burosumab clinical trials, several adverse events were described among children. Most common adverse reactions (≥10%) in burosumab-treated patients include pyrexia and transient injection site reaction; dental abscesses and periodontal disease remain common during treatment with burosumab. Other possible side effects include: cough, gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation), headache, and rash.

Early initiation of specific therapy improves the bone outcome of these individuals.

Although the clinical, biochemical and radiological picture is well characterized, the diagnostic delay of XLH is still very frequent, often after 5 years of age, thus posing patients at higher risk of long-term complications and inadequate treatment. The factors that mainly contribute to delaying the

diagnosis are the rarity of XLH and the misinterpretation of the results of laboratory tests for calcium-phosphorous metabolism; this may be further favored by a lack of careful overall assessment of clinical, biochemical and radiological signs suggestive of rickets.

This report describes an emblematic case of a girl with lower limb varus and short stature in whom the diagnosis of XLH was only made at the age of 11.

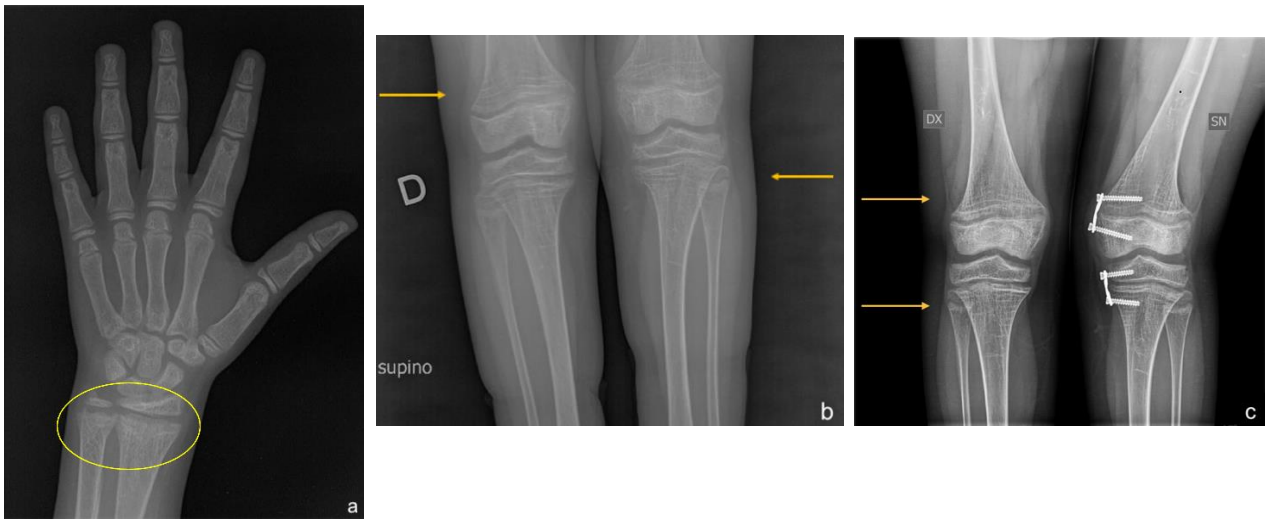
Case Report

We present the case of a 11-years-old girl who was admitted for the first time to our outpatient clinic of pediatric endocrinology for short stature and stunted growth from the age of 6. The patient was born at term, adequate for gestational age, to non-consanguineous parents.

Short stature (paternal uncles) has been reported at family history; parents' height was within normal limits (family target, TG + 0.02 SDs). At the age of 9, the girl underwent orthopaedic surgery for a valgus knee. The patient reported easy fatigue in walking and difficulty for climbing stairs both before and after surgery (score of 5 according to Numerical Rating Scale).

At the time of the first visit, she presented with a disproportionate short stature: height 125 cm (-2.41 SDS), arm span/height ratio 0.97; sitting height ratio 0.56 (>2.5 SDS). Shortened 4th and 5th metacarp, ogival palate, overlapping teeth, hyperlordosis and waddling gait were also observed. Tanner stage was B1, P2. Bone-age was 11 years, according to Greulich and Pyle method. Radiographic images of the wrist showed metaphyseal fraying with cupping of the ulna and distal radius, suggesting rickets. The same alterations were documented in the femur and tibia by evaluating pre- and post-operative X-rays. Assessing the X-ray alteration as a whole, an RSS of 7 was calculated. (Figure 1)

Fig. 1. X- ray images of wrists and knees before diagnosis. ***(a)*** *fraying and widening, with initial cup-like deformation, of the distal metaphysis of the ulna and radius (yellow circle);* ***(b)*** *fraying and widening of the distal metaphysis of the femur and the proximal metaphysis of the tibia and fibula. (yellow arrows).*



Laboratory investigations revealed hypophosphatemia, hyperphosphatasemia, diminished maximum tubular reabsorption of phosphate normalized to the glomerular filtration rate (TmPO/GFR), mild hypovitaminosis D with adequate serum level of calcium and parathyroid hormone. Normal calcium/creatinine ratio (mg/mg) in 24-hour collection of urine and absence of other disorders of tubular function indicated an isolated hyperphosphaturia. Celiac disease and hypothyroidism were excluded. Karyotype was 46, XX. The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis evaluation showed normal GH secretion (evaluated by glucagon stimulating tests). (Table 1)

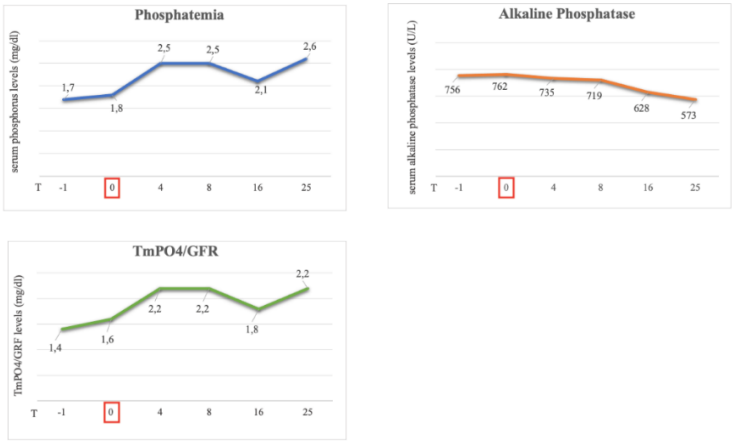
Table 1 Main biochemical findings at diagnosis

	Value	Normal Range for Age
Calcium	9,55 mg/dl	8,52 – 9,72 mg/dl
Phosphorus	1,7 mg/dl	4,66 – 6,35 mg/dl
Alkaline Phosphatase	774 U/L	138 – 436 U/L
$TmpO_4$/GFR	1,44 mg/dl	> 3,4 mg/dl
PTH	51,3 pg/ml	13 – 85 pg/ml
25OD vitamin D	20,2 ng/ml	Sufficiency > 30 ng/dl Insufficiency 20-29 ng/dl

On the basis of characteristic history data and clinical, biochemical and X-ray picture suspicion of XLH was postulated; the diagnosis was confirmed by the identification of a frameshit de novo variant in a heterozygous condition in the PHEX gene, c.1843dup (p. Thr615fs) (exon 18). Maternal and paternal analysis of PHEX did not show any abnormality. Therefore, treatment with Burosumab was started via subcutaneous injection every 2 weeks (0.8 mg/kg, gradually increased to 1.6 mg/kg).

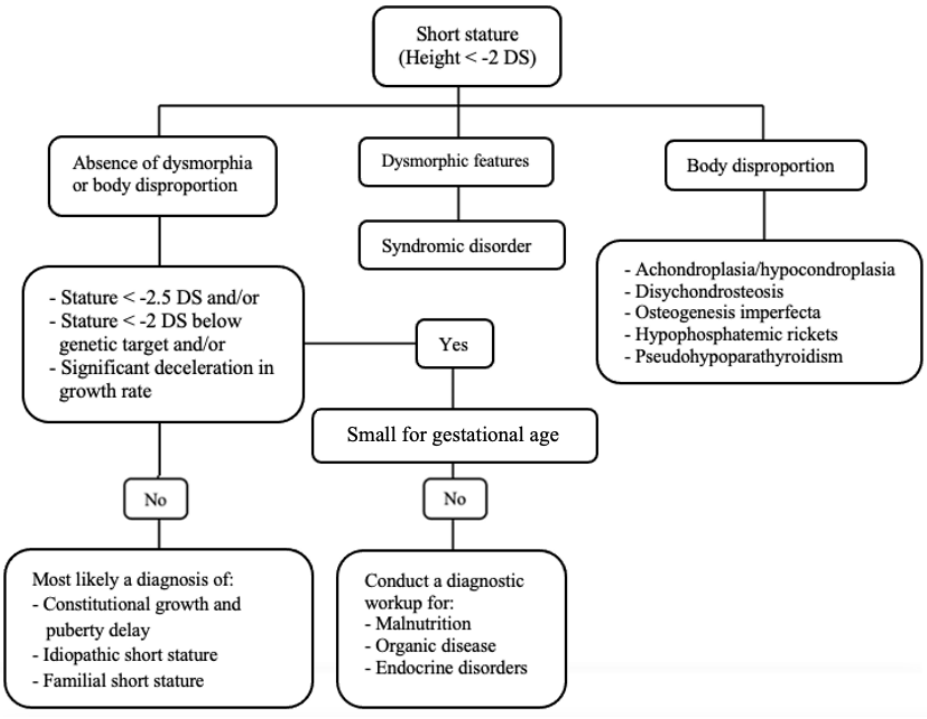
In the first 25 weeks of treatment, Burosumab determined an increase in renal tubular phosphate reabsorption, serum phosphorus levels, a reduction of alkaline phosphatase, an improvement of physical function and reducing pain (score of 2 according to NRS) (Figure 2). No adverse events have been reported. In addition, after the diagnosis, on our recommendation, the patient started dental follow-up which prescribed fixed orthodontic therapy including palatal expander for ogival palate.

Fig. 2. Biochemical parameters before and during therapy with Burosumab



x-axis (T): weeks; y-axis: serum analyte levels. The red box indicates the start of therapy with Burosumab

Fig.3. Simplified diagnostic approach to a child with short stature. *Modified by Pepe G. et al (12).*



Discussion

This report describes an emblematic case of diagnostic delay in XLH. The patient who came to our attention due to short stature had a clinical, biochemical and radiological picture strongly suggestive of XLH.

Short stature can be caused by several conditions, including primary growth disorders (syndromic or genetic defects, skeletal dysplasia) and secondary growth disorders due to endocrine or other chronic disorders (e.g. gastrointestinal or renal disease) (11). A thorough medical history and clinical examination are crucial in evaluating children with short stature. The history evaluation should include the family history to identify genetic target, cases of short stature in the family, chronic diseases or genetic syndromes; and personal history that may highlight factor influencing growth (IUGR, auxological parameters at birth, infections, organ diseases, psychosocial and cognitive development). The physical examination should aim to detect auxological parameters, including an assessment of body proportions (12). Based on the clinical suspicion, it will then be useful to perform general and specific laboratory evaluations, radiologic investigations and, in selected cases, genetic testing (13). Figure 3 shows a summary flowchart of the diagnostic pathway for short stature. Comprehensive evaluation of parameters pertaining to calcium-phosphorous metabolism, including assaying serum levels of calcium, phosphorous, magnesium, alkaline phosphatase, PTH and vitamin D, and their correct interpretation according to gender and age, must be part of the first step in the diagnostic procedure for children and adolescents with short stature.

Early diagnosis is important to correctly manage the treatable growth disorders in children, in order

to reduce complications and/or associated comorbidity and improve health, height prognosis and quality of life.

XLH is a clinically significant disease whose delayed management may result in short stature and debilitating deformities. Moreover, since hypophosphatemia is associated with bone, dental, and hearing problems, patients with XLH should be taken care of early by a multidisciplinary team, including endocrinologists, orthopedics, rheumatologists, odonatologists, physical therapists and psychologists (14).

As shown by several studies, inhibition of FGF-23 activity with burosumab is associated with an increase in renal tubular phosphate reabsorption and the correction of hypophosphatemia in children with X-linked hypophosphatemia. The improvement in phosphate metabolism has been shown to correspond to a decrease in the severity of rickets, with radiographic improvement in RSS, as well as lower pain (9; 10).

Due to the relatively recent availability of burosumab, current published experience is mostly limited to short follow-up periods (up to 64 weeks) with only one study evaluating a longer time range (160weeks).

In particular, data on height growth under burosumab are conflicting, as some studies suggest a positive effect on growth while other studies do not confirm this finding (15; 16; 17). However, current data support the importance of early treatment with burosumab to maximize height gain for children with XLH (15; 17).

In this report we point out the importance of early diagnose and accurate manage of treatable growth disorders in children, in order to reduce complications and/or associated comorbidity and improve health, height prognosis and quality of life.

Conclusions

XLH is a clinically significant disease whose delayed management can result in short stature and debilitating deformities. Evaluation and correct interpretation of calcium-phosphorus metabolism values, according to sex and age, should always be included in the diagnostic work-up of short stature, in order to avoid diagnostic delay of this rare disorder, which requires early diagnosis to obtain maximum therapeutic benefit as soon as possible.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose.
This work was not supported by any grant.

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Communicated April 6. 2024, received May 22, 2024, revised and accepted June 21, 2024, published online July 3, 2024