X-linked hypophosphatemic rickets.
What the orthopedic surgeon needs to know

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ABSTRACT

Purpose: X-linked hypophosphatemic rickets (XLH) is a rare genetic disease characterized by an increase in fibroblast growth factor 23 (FGF23) expression. The skeleton is one of the systems most affected and deformities of the lower limbs are one of the first reasons for consulting an orthopedic surgeon. The aim of the present study was to offer practical advice for a comprehensive orthopedic approach to XLH.

Materials: A literature search was conducted in PubMed, a freely available and cost-effective database. The articles included in the study were discussed by a research group with specific expertise in bone metabolism and pediatric deformities, in order to answer three fundamental questions and thus provide the orthopedic specialist with guidance on XLH: (1) How should the physician complete the diagnosis of XLH?; (2) When might a surgical procedure be recommended?; (3) What kind of surgical procedure should be performed?

Results: Sixty-three articles were included and discussed by the research group.

Conclusions: A correct and timely diagnosis of XLH is essential to appropriately manage affected patients. To complete this diagnosis a detailed medical history of the patient, a comprehensive clinical and radiographic evaluation, and specific biochemical tests are needed. Pharmacological treatment is based on supplementation of both phosphate and vitamin D, however, a monoclonal antibody that inactivates FGF23 (burosumab), has recently been introduced with promising results. Orthopedic surgery is needed in cases of moderate or severe deformities, to allow physiological growth and prevent early osteoarthritis and gait alterations. Surgical options are osteotomies and hemiepiphysiodesis, which is preferred whenever possible. Three different devices for temporary hemiepiphysiodesis are available (staples, transphyseal screws and tension band plates). Obviously, surgical procedures need an appropriate medical therapy to be effective. In conclusion, the diagnosis, treatment and follow-up of XLH require a multidisciplinary approach and a comprehensive evaluation of anamnestic, clinical and radiographic data.

KEYWORDS
Lower limb alignment, X-linked hypophosphatemic rickets, guided growth, burosumab, surgery, hemiepiphysiodesis.

Introduction

X-linked hypophosphatemic rickets (XLH) is a disease caused by a mutation of the PHEX gene located on the X chromosome. This gene encodes for a surface endopeptidase expressed on several, cells including osteocytes and osteoblasts. PHEX gene mutation is associated with increased expression of fibroblast growth factor 23 (FGF23) that, through an unknown mechanism, leads to increased phosphaturia and a deficiency of the active form of vitamin D. XLH accounts for approximately 80% of all cases of hypophosphatemic rickets with a prevalence of 1/20000 newborns. It shows complete penetrance and high clinical variability [1].

The clinical signs generally appear during the first or second year of life and involve several systems including the neurological, dental and skeletal ones. The latter is generally affected by the most striking clinical manifestations of XLH, such as cupped and flared metaphyses (giving rise to what look like

bracelets around the wrist and ankle), scoliosis and especially lower limb deformities [1]. Therefore, orthopedic surgeons are often the first physicians to examine affected children, and their approach to these patients is important in ensuring that they are appropriately managed. However, the diagnosis can be difficult. In fact, although in XLH the cortical bone is thickened, the trabeculae are larger without any signs of bone resorption, and genetic rickets is not distinguishable from the nutritional form radiographically [2,3]. Therefore, a comprehensive approach is

needed in order to complete a correct diagnosis, which is essential in order to appropriately treat these patients and avoid the development of severe deformities. The present study aims to summarize current knowledge around the orthopedic aspects of XLH, and give practical advice for such an approach.

Methods

During a preliminary meeting a research group, previously identified among orthopedics and pediatrics with specific expertise in bone metabolism, endocrinological and genetic diseases, identified three fundamental questions that could guide the orthopedic specialist dealing with XLH[1]: How should the physician complete the diagnosis of XLH?[2]; When might a surgical procedure be recommended?; and [3] What kind of surgical procedure should be performed? To answer these questions, a PubMed search was conducted by three independent researchers using the following keywords: "X-linked hypophosphatemic rickets", "skeletal angular deformities", "hemiepiphysiodesis", "guided growth" and "corrective osteotomies".

The literature search was conducted only in PubMed given that 90% of high-quality studies can be retrieved from this database, as reported by Rollin *et al.* [4]. Therefore, searching in PubMed can be considered cost-effective, and a practitioner should be able to efficiently retrieve most of the literature on a topic using it [4,5].

All articles in English, Spanish and Italian were eligible for inclusion. Articles involving subjects over 18 years of age were excluded. The references of the included articles were also reviewed. Relevant articles were identified by consensus between at least 2 out of 3 researchers. Data were extracted from the included studies, and their relevant findings were discussed by the research group and accepted if consensus was reached between at least 66.6% of the researchers.

Results

Eighty-one articles were identified after the first search. Of these, 20 were excluded because they were not considered useful for answering the proposed questions. Through evaluation of the references included in the articles, two further studies were identified. Therefore, data were extracted from a total of 63 articles and their relevant findings were discussed by the research group (Table I).

Table I List of the articles discussed by the research group.

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Discussion

Rickets is a general term that refers to a heterogeneous group of diseases characterized by defective bone mineralization that leads to replacement of mineralized with non-mineralized bone matrix (osteoid tissue) in the early stages of growth [6]. There are several causes of rickets, including nutritional ones (linked to vitamin D and/or phosphate deficiency), tumors secreting FGF23 and other phosphatonins, and other systemic diseases such as hyperthyroidism, hyperparathyroidism and sarcoidosis [4]. Genetic rickets is generally divided into "vitamin D-dependent" and "hypophosphatemic" types. The latter can be further divided into three forms: autosomal dominant, characterized by a mutation that makes FGF23 resistant to enzyme cleavage and shows incomplete penetrance and clinical variability; autosomal recessive, characterized by increased production of FGF23 and defective maturation of osteocytes; and XLH, the most frequent, which shows an X-linked dominant pattern of inheritance.

How should the physician complete the diagnosis of XLH?

The diagnosis of XLH is based on medical history, physical and instrumental examinations, family history (even though 1/3 of cases are sporadic), and mutational analysis of the gene. Very often the child comes to the attention of the orthopedic specialist because of lower limb malalignment, which could affect 94.8% of patients with XLH [1].

The medical anamnesis is useful for understanding the onset of the deformity, its history (whether it was preceded by a trauma, whether it is improving or worsening), and its association with other signs or symptoms. The lower limb malalignment might be angular (valgus or varus knee) or torsional (retro-anteversion of the femur and extra-internal rotation of the tibia) [1]. However, these conditions can also represent stages in normal growth. Therefore, it is important to be able to recognize pathological varus and valgus knees, and also to differentiate ones associated with rickets from ones associated with other disorders [7]. The physical examination should be conducted with the patient appropriately positioned (namely with the patella of both limbs in the frontal plane) in order to reduce the influence of femoral anteversion and adipose tissue which could lead to apparent malalignment (to reduce the femoral anteversion and fat tissue contribution to the knee malalignment that could lead to an apparent malalignment [7]). When the patient's position is considered appropriate, the orthopedic specialist should evaluate the presence and degree of the malalignment, calculating both the intercondylar and intermalleolar distances. If pathological lower limb malalignment is observed, full-length antero-posterior and lateral X-rays are needed.

Correct alignment of the lower limbs is demonstrated by the presence of a "physiological valgus angle" between the anatomical axis of the femur and the tibia (6° – 8°) [3]. However, comprehensive evaluation of lower limb alignment needs a standardized analysis of the anatomical angles of both the femur and the tibia (see Fig. 1) [3,8].

The first radiological parameter to be evaluated is the mechanical axis deviation (MAD), defined as the deviation of the knee center of rotation from the lower limb mechanical axis [3] (see Fig. 1). Physiologically, the knee center of rotation should be located medially to the mechanical axis and the MAD should not be greater than 8 mm. Any deviation from this distance will result in lower limb malalignment (varus knee in the presence of MAD values > 8mm; valgus knee when the MAD is < 8 mm). Obviously, the MAD tends to change as the child grows, going from positive deviation values (varus knee) during the first two years of age to negative ones (valgus knee) up to six years of age, when, in general, physiological alignment is reached [3]. However, an orthopedic surgeon should always consider malalignment radiographically pathological if the MAD is greater than 8 mm, especially in children over 2 years of age.

When malalignment is observed, an appropriate description of the deformity is required and this should be obtained by evaluating the joint orientation angles on both the full-length antero-posterior and the lateral lower limb radiographs (see Figure 1 and Table II for further details) [3,8,9].

Furthermore, a careful evaluation of the morphology of the physis is recommended to identify the characteristic changes

Figure 1 Full-length lower limb X-ray of a 4-year-old patient with hypophosphatemic rickets.
Note the widening, cupping and indistinct margins of the distal femoral and proximal tibial physes. On the right side, the mechanical axis of the lower limb (straight line in red) and the evaluation of its distance from the knee center of rotation (MAD). On the left side, joint orientation angles of the femur (in blue) and the tibia (in green) calculated with respect to the mechanical axis of each bone.
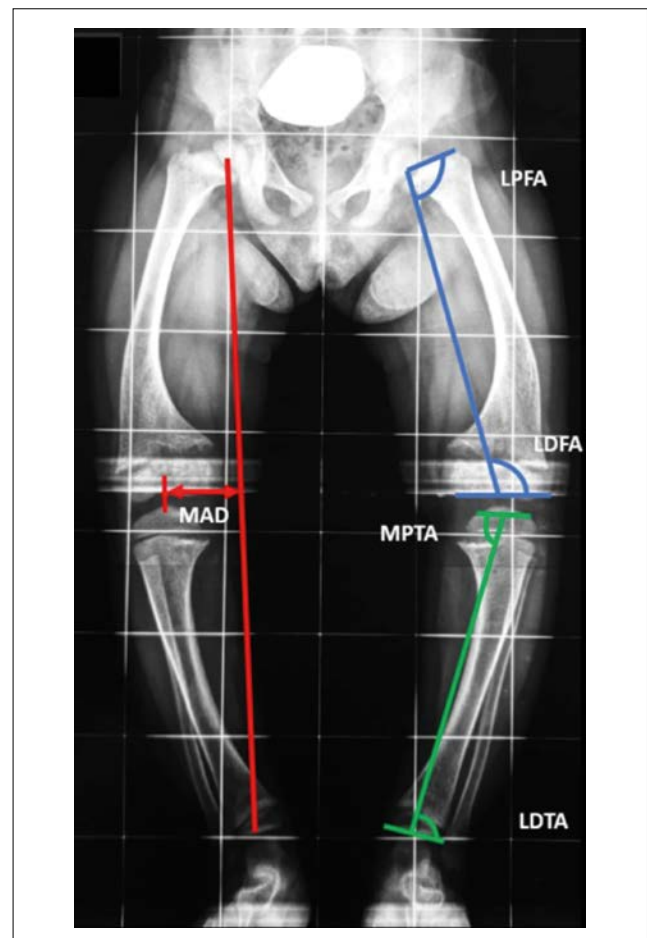
Table II Joint orientation angles.

FRONTAL PLANE (ANTERO-POSTERIOR VIEW)		
ANGLE	**DEFINITION**	**NORMAL VALUES**
Lateral proximal femoral angle (LPFA)	The angle between a line connecting the hip center of rotation and the apex of the greater trochanter and the mechanical or anatomical axis of the femur	90° (85°–95°)
Lateral distal femoral angle (LDFA)	The lateral angle between the distal femoral joint line and either the mechanical or anatomical axis of the femur	88° (85°–90°)
Medial proximal tibial angle (MPTA)	The medial angle between the proximal tibial joint line and either the mechanical or anatomical axis of the tibia	87° (85°–90°)
Lateral distal tibial angle (LDTA)	The lateral angle between the distal tibial joint line and either the mechanical or the anatomical axis of the tibia	89° (86°–92°)
SAGITTAL PLANE (LATERAL VIEW)		
ANGLE	**DEFINITION**	**NORMAL VALUES**
Posterior proximal femoral angle (PPFA)	The angle between a mid-diaphyseal line of the femoral neck and a line that crosses the proximal physis	90°
Anterior neck shaft angle (ANSA)	The angle between the mid-diaphyseal line of the femoral neck and the mid-diaphyseal line of the proximal part of the diaphysis	170° (165°–175°)
Posterior distal femoral angle (PDFA)	The angle between the distal femoral joint line and the mid-diaphyseal line of the distal femur	83° (79°–87°)
Posterior proximal tibial angle (PPTA)	The angle between the proximal joint line and the mechanical axis of the tibia	81° (77°–84°)
Anterior distal tibial angle (ADTA)	The angle between the distal articular joint line and mechanical axis of the tibia	80° (78°–82°)

associated with rickets: growth plate widening and abnormal configuration of the metaphysis (indistinct margins, widening and cupping) [10,11]. If rickets is suspected, a radiograph of the distal radius is recommended in order to look for these metaphysis abnormalities in this area, too, and to calculate the Rickets score [10-12]. This score, which ranges from 0 to 10, is a useful tool for the follow-up of the patient with rickets, giving an idea of the severity of the disease [10]. Computerized bone mineralometry (CBM), a method of measuring bone mineral density (BMD), has been proposed as a diagnostic and monitoring tool for XLH because it is simple and quick to use, and painless [8].

However, the interpretation of pediatric dual-energy X-ray absorptiometry scans is complex due to the continuous changes in the geometry of the growing skeleton. This can potentially make the values obtained misleading, especially in the presence of growth problems like those observed in rickets. In fact, children with XLH show an increase in bone mineral apparent density (BMAD, a volumetric measure of bone density) of the spine compared with the femoral neck, probably because the disease affects the growth of the upper and lower limbs more than that of the spine [8]. CBM could be more useful for assessing, as part of a comprehensive evaluation, the associated clinical manifestations, like short stature, dental abscesses and head deformities, even though this test, also in adults with XLH osteomalacia, is used more to assess response to therapy than to make a diagnosis. Even in this case, however, doubtful values can be observed, as the BMD is often exceptionally high in the lumbar spine of these patients because of extra-skeletal calcifications and enthesopathies [13,14]. The diagnosis of XLH might be confirmed through evaluation of certain biochemical parameters that are typical-ly altered in this disease, such as hypophosphatemia (in this case, the evaluation must be age-adjusted), increased serum alkaline phosphatase and FGF23 levels, and phosphaturia. Although the serum levels of FGF23 may be up to five times the normal values, and a cut-off point for the diagnosis was set at 30 ng/ml, low values could also be observed in XLH [2]. In any case, whenever XLH is suspected or biochemically confirmed, a consultation with a pediatrician or endocrinologist with specific expertise is recommended.

Figure 2 Comparative antero-posterior distal radius X-rays showing the physeal changes (indistinct margins, widening and cupping) observable in figure 1 (same patient).
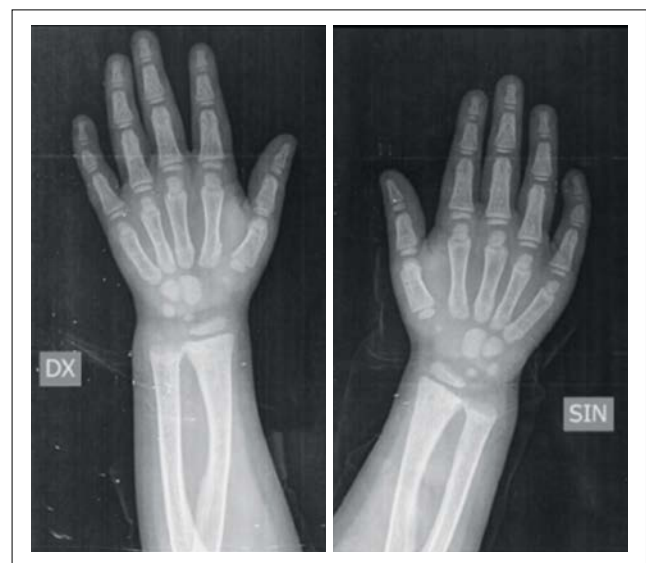
When might a surgical procedure be recommended?

Traditionally, medical management of XLH was based on early supplementation of oral phosphate and vitamin D. This kind of approach was demonstrated to be effective only on some of the manifestations of the disease, such as dental alterations and reduction of definitive height [15]. However, up to two-thirds of children with XLH submitted to this kind of treatment required surgical intervention for lower limb deformities [2]. The recent advent of burosumab has marked a pivotal change in the management of XLH 16. Approved in 2018 by the European Medicines Agency [17], burosumab is a monoclonal antibody that binds and neutralizes FGF23, reducing its effects on the bone [18]. FGF23 has both direct and indirect actions on bone metabolism and growth: it inhibits the proliferation of chondrocytes in the metaphysis, reduces the levels of phosphate and calcium (inorganic components of the bone matrix), and inhibits the conversion of vitamin D into its active form [2,9]. Therefore, burosumab might reduce the severity or even prevent the development of skeletal deformities, while improving the effectiveness of the necessary surgical procedures. Non-responders to the supplementation have been seen to need up to nine surgical procedures to correct the deformities [19], with a recurrence rate of 27% after both closing- and opening-wedge osteotomies [20].

Correction of angular deformities of the lower limbs must be performed in order to improve the patient's quality of life and limb function. In fact, a severe lower limb angular deformity could limit a child's walking and participation in sports activities, and lead to abnormal joint loading with the occurrence of early osteoarthritis in the compartment more affected by the deformity [18,20,21]. Moreover, valgus knee is frequently associated with patellofemoral syndrome [22]. Use of traditional orthopedic footwear does not seem to be useful for the correction of angular deformities of the lower limbs, and the only demonstrated effective conservative treatment is that based on orthoses with thrusts and counter-thrusts in the area of the deformity [23].

In XLH, however, it should be noted that this kind of approach would not be effective without appropriate medical management of the disease, and that patient compliance tends to become progressively worse from the age of 5 years [24].

What kind of surgical procedure should be performed?

The surgical procedures used for the correction of angular lower limb malalignments are hemiepiphysiodesis and osteotomies. Hemiepiphysiodesis refers to procedures based on the concepts of "guided growth", related to the mechanical manipulation and modulation of bone growth [25]. These concepts were first introduced in 1862 by Heuter, who stated that the growth of the epiphysis depends, among other things, on the pressure to which it is exposed (with increased pressure slowing down growth, and decreased pressure promoting it) [26]. In 1933, Phemister et al. first described the surgical procedure of hemiepiphysiodesis as permanent growth arrest brought about by a partial physeal ablation [27]. Nowadays, most authors prefer temporary hemiepiphysiodesis, which is based on the use of different fixation devices that straddle the physis on the convex side of the deformity with the ultimate aim of slowing down the growth of the more active side, while promoting recovery of the less active one [26]. This surgical procedure was proposed by Blount and Clarke using staples [28], the aim being to arrest growth under the staples, thereby allowing gradual correction of angular deformities. Reported complications associated with the use of staples were loss of fixation, breakage or migration of the staples (especially if the epiphysis was too small), and rebound effects [26,29]. Staple-related complications, including rebound effects, were also observed by both Novais and Stevens and Stevens and Klatt [21,30] in their series of patients with XLH. This observation led Novais and Stevens to prefer the tension band plate (TBP) to treat this kind of patient [21].

The TBP is a pre-shaped two- to four-hole plate known as an eight-plate. The plate, which has a long lever arm, acts as a focal hinge at the edge of the physis. Reported TBP-related complications are infections, screw breakage, partial correction and overcorrection [26,29,31]. In the series by Stevens and Klatt, the authors did not report any complications with the use of eight-plates in XLH [30].

Metaizeau et al. described percutaneous epiphysiodesis using transphyseal screws (PETS) [32]. The authors used cannulated screws across the physis. These screws are stronger than staples and provide a rigid temporary hemiepiphysiodesis that gives faster correction (albeit starting later) using a percutaneous procedure. Under fluoroscopic guidance, the physis is crossed using a K-wire properly positioned in the center of the sagittal plane, i.e., in the external and the internal quarter of the coronal plane for genu varum and valgum, respectively. The positioning of the K-wire is a pivotal phase of the procedure because it serves as a guide for the cannulated screw; mispositioning could result in final malalignment [32,33]. One of the main complications of this surgery is the possibility of premature growth arrest [29]. To the best of our knowledge, no studies have been published on the use of PETS in XLH.

The three guided-growth techniques reported (hemiepiphysiodesis with staples , TBP and PETS) were directly compared for the treatment of lower limb discrepancy; less pain and faster operative time and recovery were observed with PETS, while no clear differences were reported in terms of complications [34].

Shapiro et al. compared TBD and PETS for the correction of angular deformities. They observed that the former was associated with faster correction, while the complication rate was comparable [31].

Correction performed through guided-growth techniques can be considered satisfactory when the tibio-femoral angle is in the normal range and its correction is maintained after fixation removal until skeletal maturity. Of note, if appropriately performed, hemiepiphysiodesis may also aid in correcting diaphyseal deformities [30]. In order to improve outcomes, it is advisable to avoid activities with excessive axial loading of the lower limbs, like jumping and running, during the first two weeks after the surgery and clinical and radiographic follow-up should be performed at regular intervals in a multidisciplinary setting [31,35].

No specific criteria have been proposed to guide the start of guided-growth treatment in XLH [19], but an important factor that may have an impact on the final outcomes is the age at which the surgery is performed. Generally, the varus knee

should be corrected from 4 years of age, while the valgus knee from around 10 years of age, as the deformity is quite stable at this stage. However, Novais and Stevens suggested that a guided-growth procedure could be started before 10 years of age in XLH [21].

If "guided growth" led to unsatisfactory correction, the center of the deformity does not involve the growth plates, residual growth is insufficient, or the deformity presents an angle > 20°, corrective osteotomies might be required [36]. Corrective osteotomy should be performed at the center of the deformity — this is because the farther from the center it is performed, the wider the translation between the two fragments will be [9]. However, in varus knee, osteotomy very often involves the proximal portion of the tibia, while in valgus knee it involves the distal portion of the femur [37,38]. There are two types of osteotomy: opening-wedge (with the need of a bone graft) and closing-wedge (based on the subtraction of a piece of bone). Osteotomy is followed by deformity correction (acute or gradual) and fixation (internal and external, respectively). Gradual correction with external fixators reduces the rate of complications associated with the acute type (i.e. neurovascular lesions, compartment syndrome, delayed union, etc.), and provides a better correction in cases with multiplanar deformities [37,38]. However, gradual correction with external fixators is not free of complications, and the main ones reported with its use are: fractures occurring during or after the correction, osteotomy nonunion and healing delays, osteomyelitis, recurrence, and residual deformity. Of note, the use of external fixation may be problematic before 8 years of age due to the lack of cooperation and motivation of patients [39]. In these cases, too, patients must be followed up regularly in a multidisciplinary setting.

Considering the unpredictability of bone metabolism in XLH and the need for medical therapy adjustments, close collaboration with an expert pediatric endocrinologist is mandatory in both types of surgery. However, in our opinion, the availability of burosumab will improve the outcomes of guided-growth techniques, and thus reduce the need for corrective osteotomies.

In conclusion, XLH is a disease that requires a multidisciplinary approach throughout the spectrum of its diagnosis, treatment and follow-up. The orthopedic surgeon is frequently the first physician involved in the identification of this disease because of the frequent occurrence of angular deformities of the lower limbs. However, to complete the diagnosis, detailed personal and family histories must be collected, and appropriate radiographic and laboratory tests must be performed and evaluated, also involving an expert pediatric endocrinologist in the process. The orthopedic management is generally focused on the prevention and treatment of lower limb deformities through both conservative and surgical approaches. Surgery in XLH needs careful preoperative planning and close follow-up. In our opinion, when surgery is indicated, guided-growth techniques should be preferred whenever possible, and the availability of a targeted therapy would improve their outcomes, reducing the need for corrective osteotomies. However, starting burosumab early might reduce the severity or even prevent the development of limb deformities, potentially leading to a change in the orthopedic approach to XLH.

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Study limitations: Our study presents some limitations, mostly related to the quality of the included articles. Moreover, the use of a single scientific database could mean that other relevant articles are missed. However, the reliability, and cost-effectiveness of the PubMed database made us confident of the relevance of the discussed literature.

Conflict of Interest: The authors declare that there is no conflict of interest