



Outcomes of orthopedic surgery in a cohort of 49 patients with X-linked hypophosphatemic rickets (XLHR)

A Gizard¹, A Rothenbuhler^{2,3,4}, Z Pejin⁵, G Finidori⁵, C Glorion⁵, B de Billy¹, A Linglart^{2,3,4,6} and P Wicart^{3,5}

¹Department of Pediatric Orthopedic Surgery, Besançon University Hospital, Paris, France

²APHP, Department of Pediatric Endocrinology, Bicêtre Paris Sud, Le Kremlin Bicêtre, France

³Reference Center for Rare Disorders of Calcium and Phosphate Metabolism, Le Kremlin Bicêtre, France

⁴Plateforme d'Expertise Paris Sud Maladies Rares and Filière OSCAR, Bicêtre Paris Sud, Le Kremlin Bicêtre, France

⁵APHP, Department of Pediatric Orthopedic Surgery, Necker Hospital, Paris, France

⁶INSERM U1169, Hôpital Bicêtre, Le Kremlin Bicêtre, et Université Paris-Saclay, Le Kremlin Bicêtre, France

Correspondence should be addressed to A Linglart or P Wicart
Email
agnes.linglart@aphp.fr or p.wicart@aphp.fr

Abstract

Background: X-linked hypophosphatemic rickets (XLHR) is due to mutations in *PHEX* leading to unregulated production of FGF23 and hypophosphatemia. XLHR is characterized by leg bowing of variable severity. Phosphate supplements and oral vitamin analogs, partially or, in some cases, fully restore the limb straightness. Surgery is the alternative for severe or residual limb deformities.

Objective: To retrospectively assess the results of surgical limb correction in XLHR (osteotomies and bone alignment except for 3 transient hemiepiphysestasis).

Methods: We analyzed the incidence of recurrence and post-surgical complications in 49 XLHR patients (29F, 20M) (mean age at diagnosis 6.0 years (± 7.1)).

Results: At first surgery, the mean age was 13.4 years (± 5.0). Recurrence was observed in 14/49 (29%) patients. The number of additional operations significantly decreased with age (2.0 (± 0.9), 1.7 (± 1.0) and 1.2 (± 0.4) in children <11 years, between 11 and 15, and >15 years; $P < 0.001$). Incidence of recurrence seemed to be lower in patients with good metabolic control of the rickets (25% vs 33%). Complications were observed in 57% of patients.

Conclusion: We report a large series of surgical procedures in XLHR. Our results confirm that phosphate supplements and vitamin D analog therapy is the first line of treatment to correct leg bowing. Surgery before puberty is associated with a high risk of recurrence of the limb deformity. Such procedures should only be recommended, following multidisciplinary discussions, in patients with severe distortion leading to mechanical joint and ligament complications, or for residual deformities once growth plates have fused.

Key Words

- ▶ X-linked hypophosphatemic rickets
- ▶ osteotomy
- ▶ PHEX
- ▶ hemiepiphysestasis
- ▶ genu varum
- ▶ genu valgum

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Introduction

X-linked hypophosphatemic rickets (XLHR) is the most frequent cause of genetic and heritable rickets. It is caused by mutations damaging the function of the endopeptidase encoded by the *PHEX* gene located on the X chromosome (1). The *PHEX* protein is expressed in the mineralized

tissues, i.e. the bone matrix and the teeth. When *PHEX* is impaired, fibroblast growth factor 23 (FGF23) is produced in excess, leading to renal phosphate wasting and insufficient production of 1,25(OH)₂ vitamin D, thereby altering the function of target organs including the bone



and the growth plate (2). Children affected with XLHR present with rickets, osteomalacia, enlarged joints, bone pain, growth retardation, abnormal mineralization of the teeth and leg bowing (3).

The last of these usually appears when the child starts to walk; it may be of variable importance and no predictive factors have been identified (Fig. 1). In most patients, the deformity involves the frontal plan leading to *genu varum* or *genu valgum* or the combination of both (Figs 1 and 2). There is often concomitant bone twisting (4, 5, 6, 7, 8).

The current treatment for XLHR comprises phosphate supplements in multiple daily doses and active vitamin D analogs in order to heal the rickets and the osteomalacia, restore the growth velocity and straighten the legs. To achieve these objectives, the treatment requires a rigorous follow-up and regular adjustments based on weight, and other growth measures, and biochemical parameters. In addition, early initiation of the medical treatment has been associated with better outcomes (3, 8, 9, 10, 11).

Orthopedic corrective surgery is indicated if there is marked leg bowing, with immediate functional consequences or long-term threats to the joints. Usually, the bone deformities are corrected through one or multiple osteotomies associated with internal or external osteosynthesis (4, 12, 13, 14, 15). Some surgeons progressively correct the angles by transient hemiepiphysectomy (4, 16, 17). Recurrence of the bowing has frequently been reported (4, 6, 7, 15, 16, 17, 18). As for every surgery, unexpected consequences have been described, these including pseudarthrosis at the site of the osteotomy (7, 14, 17, 18, 19) and pathological fractures (6, 15, 17).

The main aims of our retrospective multicenter study were 1- to evaluate the long-term results of the orthopedic surgery performed during childhood in XLHR patients and 2- to identify factors predictive of the course.

Methods

Patients were included in the study if: they had a clinical and biochemical profile compatible with the diagnosis of XLHR, when possible, the diagnosis being confirmed through a genetic analysis; and they underwent at least one surgery of the lower limbs between 1974 and 2014 in one of the 4 centers. The first surgery occurred in 11 patients between 1974 and 1983, in 10 patients between 1984 and 1993, in 8 patients between 1994 and 2003 and in 20 patients between 2004 and 2014.

We included all patients affected with XLHR who underwent at least one orthopedic surgery in Necker hospital, Paris and in the Centre Hospitalier Universitaire, Besançon, France. Patients were identified through the Reference Center of Rare Diseases of Calcium and Phosphate Metabolism that encompasses both surgical departments.

We collected data related to age at diagnosis, bone phenotype, surgery, active vitamin D and phosphate supplement therapies and alkaline phosphatase level at the last visit.

The metabolic control of the disease was assessed by the bone deformity, i.e. the distance measured between the knees or the ankles, and the alkaline phosphatase level at the last visit. Unfortunately, too many data were missing to include this parameter in the analysis.

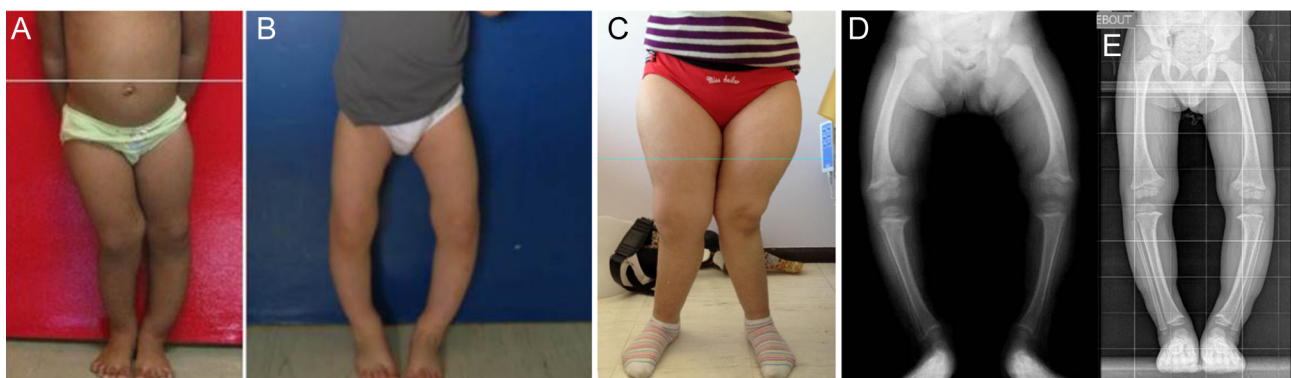


Figure 1

(A, B and C) Leg bowing in 3 patients affected with XLHR (mutation in PHEX). Note the *genu varum* and *genu valgum* in (A), *genu varum* in (B) and *genu valgum* in (C). (D and E) X-rays of the lower limbs in 2 XLHR children at the time of diagnosis at the age of 4 years (D) and 3 years (E).

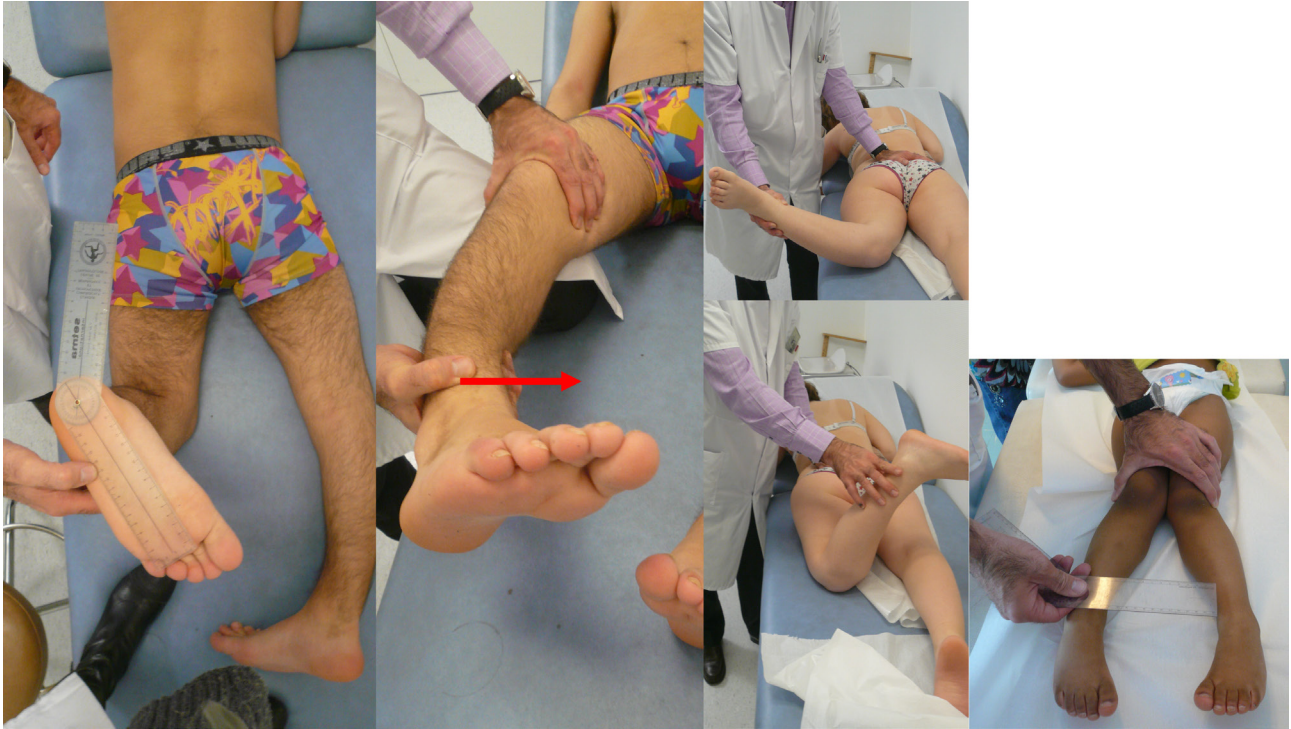


Figure 2
Bone deformity and torsion of the legs shown during the examination of the patients.

The local institutional review board of the Center of Reference of Rare Diseases of Calcium and Phosphate Metabolism approved the study. All patients and parents consented to this retrospective study. Written informed consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

Differences between groups were assessed using unpaired nonparametric tests; for qualitative data, comparisons were performed with a χ^2 test. The significance threshold was set at $P \leq 0.05$. Statistical analyses were carried out using GraphPad PRISM (v6). All values are shown as mean \pm s.d.

Results

Patients

Forty-nine patients (20 girls and 29 boys) affected with XLHR were included in this four-center retrospective study. At diagnosis, the mean age was 6.0 years (± 7.1) (Table 1). A total of 32 (out of the 49) patients (65%) presented with a *genu varum* at the time of the first surgery; the mean distance measured between the knees while lying flat (hereafter called the intercondylar distance) was 11.1 cm

(± 6.4). The remaining patients (35%) presented with a *genu valgum*; the mean distance measured between the ankles (hereafter called the intermalleolar distance) was 14.3 cm (± 5.7) (Fig. 2). The leg deformity was asymmetric in 20/49 patients. Six and two patients presented with a knee hyperlaxity and a patella sub-dislocation at the time of the first surgery, respectively.

Prior to surgery, most of the patients (42/49) received the current standard therapy for XLHR, i.e. oral vitamin D analogs and phosphate supplements. Seven patients were not appropriately treated for several reasons, i- the diagnosis had not been made, ii- the patients were operated on before 1980 (active vitamin D only having become available in France in 1975) or iii- the active vitamin D was not available in their country of origin. Only around half of the patients (29/49) had a value of alkaline phosphatase within the normal or close to the normal range at the time of their last assessment.

We divided the 49 patients into 3 groups based on age at first surgery. Group A comprised 13 patients (26%) who had their first surgery before puberty, i.e. <11 years. Group B comprised 20 patients (41%) who had their first surgery during puberty, i.e. >11 years and <15 years. Group C comprised 16 patients (33%) who had their first surgery after puberty and after the end of growth, i.e. >15 years. In

Table 1 Characteristics of the patients.

	Group A 1st surgery <11 years	Group B 11 years > 1st surgery <15 years	Group C 1st surgery >15 years	Comparison of groups
Number of patients (%)	13 (26)	20 (41)	16 (33)	
Patients with an identified mutation in the <i>PHEX</i> gene (N)	7	17	7	
Patients with alkaline phosphatase levels within the normal range at the last visit (N)	5	11	12	
Age at diagnosis (years)	5.0 (±4.9)	6.3 (±8.3)	6.6 (±8.3)	NS, P=0.967
Sex (M/F)	5/8	8/12	9/7	
Age at 1st surgery (years (±s.d.); min; max)	7.7 (±2.7); 3.1; 10.8	13.2 (±1.3); 11.0; 14.9	18.3 (±4.6); 15.1; 31.5	P<0.0001
Age at last visit (years (±s.d.))	26.0 (±13.1)	21.6 (±9.7)	23.1 (±6.8)	NS, P=0.388
Z-Score of height at last visit (mean (±s.d.))*	-3.3 (±2.1)	-2.3 (±1.4)	-2.6 (±1.8)	NS, P=0.608

*1, 4 and 1 patients in group A, B and C received growth hormone for their short stature, respectively; NS for not significant.

addition, in each group, we particularly closely examined the cases of patients with uncontrolled metabolic rickets versus those with controlled disease.

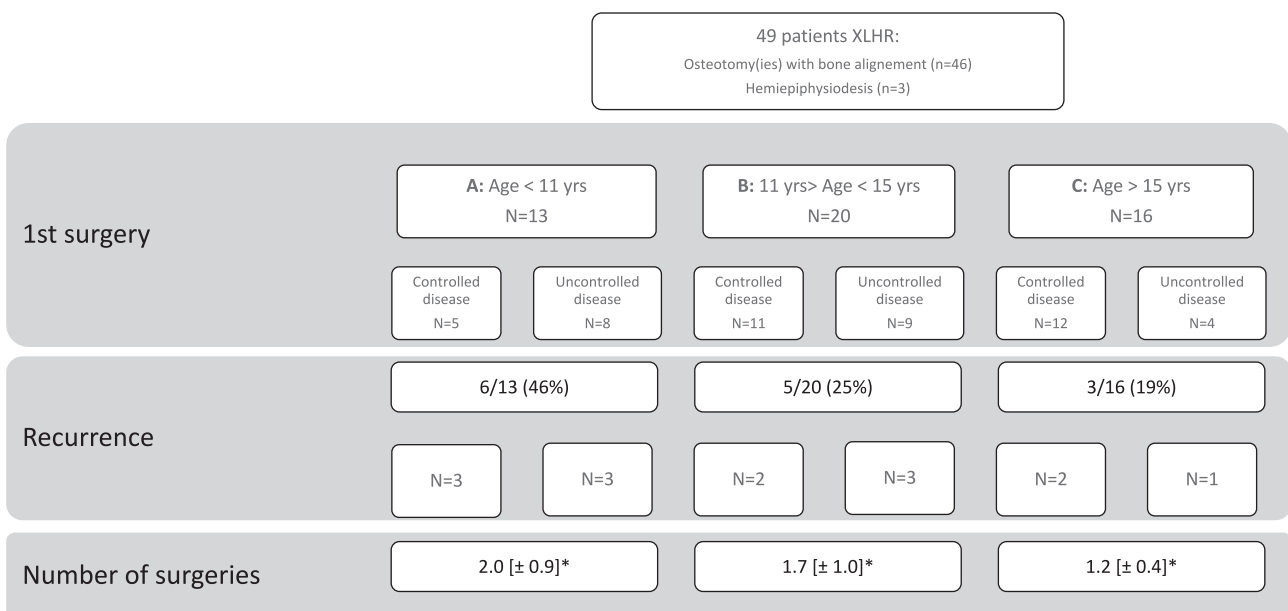
Surgery

Considering the entire cohort, the mean age at first surgery was 13.4 years (±5.1) (Fig. 3). Overall, 46/49 patients underwent an osteotomy with correction and fixation to restore the alignment of the bones (Fig. 4A and B). The correction of the deformity was either progressive or acute using external or internal fixation. Overall, 22 (45%) and 36 (74%) patients underwent a femoral and a tibial osteotomy, respectively. In 16 patients, both osteotomies were done concomitantly. The

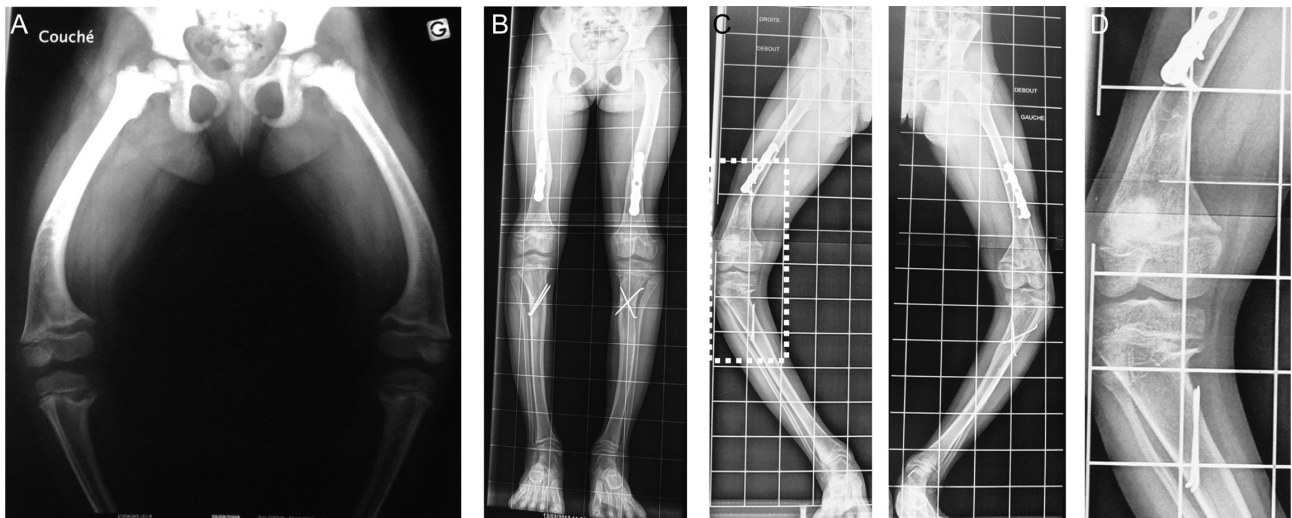
osteotomies achieved an effective correction of lower limb deformity with post-operative inter-condylar and malleolar distances of less than 2cm. Only three patients had a transient unilateral hemiepiphysiodesis, a technique based on the principle of guiding the growth. This procedure did not provide significant limb axis correction.

We were able to retrieve follow-up data on the patients for an average period of 9.4 years after their first surgery.

Overall, 14 patients had recurrence after their first surgery, in a similar manner to the initial bone deformity in all cases (9 in *varus* and 5 in *valgum*). The recurrent distortion occurred in the close vicinity of the osteotomy, i.e. proximal in the case of femoral osteotomy and distal in the case of tibial osteotomy (Fig. 4C). However, in

**Figure 3**

Flow chart of the surgical operations and course over time. Patients are divided into 3 groups (A, B and C) according to their age at first surgery. The number of patients with controlled or non-controlled rickets is shown. Overall, the mean number of operations per patient is shown in the bottom panel. Statistically significant differences between the three groups are indicated (*).

**Figure 4**

Post-osteotomy changes and complications in a patient with severe rickets due to XLHR. (A) X-rays of the legs prior to the first surgery (age 7.9 years). (B) Correction of the leg deformity immediately after the surgery. (C) Recurrence of the *varum* below the femoral osteotomy (age 9.5 years). (D) Enlarged picture of the femoral and tibial physis (framed in (C)) showing the medial epiphysiodesis although the surgery was performed at distance from the physis.

three patients, the recurrence of the bowing was caused by a bilateral spontaneous asymmetric epiphysiodesis occurring at a distance from the initial surgery site. In two patients, the epiphysiodesis was located at the medial compartment from the proximal tibial metaphysis (Fig. 4D). In one patient, it affected, the medial compartment of the distal tibial physis.

The rate of recurrence appeared lower, although not significantly, when patients were older at first surgery (46, 25 and 19% in groups A, B and C, respectively) (Fig. 3). In addition, the number of iterative surgical procedures was inversely correlated with age at first surgery ($2.0 (\pm 0.9)$, $1.7 (\pm 1.0)$ and $1.2 (\pm 0.4)$ in groups A, B and C, respectively; $P=0.0221$). Medical control of the rickets assessed by the ALP level at the last follow-up only showed a tendency to favor a better outcome (25 and 33% of recurrence in patients with a metabolic controlled vs uncontrolled rickets, respectively). Patients with an intercondylar distance below 12 cm (median of intercondylar distances in this series) had similar outcomes (recurrence, number of surgeries and complications) than those with an intercondylar distance superior to 12 cm. In two patients, the surgical hemiepiphysiodesis, performed at the age of 11.5 and 12 years, did not improve the leg shape at all. Both patients underwent additional surgeries thereafter to correct their leg deformities. In one patient, the improvement was described as moderate at 6 months after the surgery. The patient did not go through any additional surgical intervention.

In average, patients who underwent their first surgery between 1974 and 1983 ($n=11$), when compared to patients operated between 2004 and 2014 ($n=20$), were diagnosed later for XLHR, showed more severe bone deformities, had their first leg surgery earlier, went through a larger number of limb surgeries, experienced a greater rate of recurrence and complications and had a shorter final height (Supplementary Table 1, see section on supplementary data given at the end of this article).

Twenty-eight (57%) patients experienced at least one surgery-related complication, including recurrence (18/49 if we exclude the recurrences), leading to an additional operation in 25% of cases. The mean number of complications in these 28 patients was $1.7 (\pm 0.5)$. Neither age at first surgery nor medical control of the rickets was associated with the occurrence of these complications. The rate of complications was 25, 14, 17 and 100% after one, two, three or more operations, respectively. Apart from recurrences, the reported complications were pseudoarthrosis, fractures, infection, ossification around a pin, early arthrosis and hypoesthesia in the area of the inferior tibial nerve.

Discussion

Our objective herein is to report our experience in the limb surgery of patients affected with XLHR to identify factors predictive of the outcomes and highlight the specific characteristics of this type of surgery in the context of XLHR.

To our knowledge, this cohort of patients with XLHR who have undergone surgery is among the largest reported so far (5, 6, 7, 8, 12, 13, 14, 15, 18, 19). It would be reasonable to expect that patients with this condition who require surgery to be the most severely affected. In line with this, the mean final height of the entire cohort is $-2.7 (\pm 1.7)$, less than the previously reported mean adult height in XLHR (10, 11, 20, 21, 22). Noteworthy, the mean age at diagnosis of this cohort is higher than what is usually reported in series of XLHR patients. This may be due to the selection of patients restricted to those who required surgery. Eight out of 49 patients were diagnosed after the age of 10 years, including 4 patients who underwent surgeries before the diagnosis of the disease was made.

One major finding of this study is the high rate of recurrence after the first surgery (29%), confirming the reports in smaller case series (27% in (17, 18, 19), 25% in (7) and 90% in (4, 6, 15)). Overall, the risk of recurrence appears to be related with young age at first surgery, as demonstrated by the inverse association between age at first surgery and the number of operations, and the decreasing rate of recurrence in groups A, B and C. As above, this result is in accordance with previous published reports (4, 5, 6, 17). For instance, in a series of 10 XLHR patients, Petje and coworkers described 90% of recurrences after first surgery (average age 8 years and 10 months) and 60% after second surgery, leading to a mean of 3.7 procedures per patient (6).

In our series of XLHR patients, the control of the rickets, assessed by the level of alkaline phosphatase at the last follow-up visit, was not associated with the rate of recurrence or with the complications. Our analysis may have been limited because we could not assess the metabolic control at the time of the 1st surgery. In contrast, Rubinovitch and coworkers reported a strong effect of the biochemical control of the disease in preventing recurrences in a series of 10 XLHR children. Notably, the assessment of the metabolic control of the disease in their publication was more stringent than ours, as it included X-rays and bone biopsy patterns, alkaline phosphatase level, growth rate and progression of the bone deformity (18). Other groups have described similar experiences (8, 19). XLHR is a metabolic disorder associated with increased circulating FGF23 levels, and hence, phosphate wasting. Ineluctably, in the absence of medical treatment, the bone is abnormally mineralized and the growth plate is disorganized because of the decreased apoptosis of the chondrocytes. Therefore, following surgery, open physes are prone to rickets, and hence bone deformities if the

medical therapy is not sufficient. The findings of our study might have been limited by i- the assessment of the metabolic control, ii- the size of the sample and iii- the retrospective analysis of the data.

We report here, for the first time, three cases of spontaneous post-surgical epiphysiodesis, likely reflecting the severity of the disease affecting the physis in the absence of adequate medical therapy. In two studies, premature fusion of the pathological growth plates was suspected. Rohmiller and coworkers proposed that the short stature of patients that had been operated on might be due either to the surgical procedure itself or to the severity of the disease (7). In a large series of 47 patients, Popkov and coworkers observed that some patients who underwent osteotomies and internal nailing had newly formed deformities in the distal femoral and proximal tibial metaphysis (15).

Hemiepiphysiodesis is an alternative procedure to osteotomy, which could limit the bone deformity in young patients (16). However, in accordance with Eyres and coworkers, we observed poor corrections and a high rate of recurrence associated with this technique (14), limiting its use in daily practice.

To limit the number of surgical procedures per patient, and hence the number of complications, based on our results and a critical analysis of the literature, we recommend close monitoring of patients in the context of multidisciplinary care involving the medical team responsible for adjustment of the phosphate supplements and vitamin D analogs and the radiologist responsible for imaging the bones and assessing the degree of the leg deformities. As the current medical treatment allows a complete or a partial restoration of the leg shape (8, 19), it is of utmost importance to diagnose the disease as early as possible, start the medical treatment as soon as the diagnosis is established and obtain an optimal metabolic control of the rickets, i.e. lack of bone pain, growth velocity normal for the age, normal or near-normal alkaline phosphatase levels and absence of signs of active rickets on X-rays of the physes. In XLHR patients, it might be beneficial to delay the surgery to closer to the end of the growth, to obtain this metabolic control of the disease and perform only one corrective surgery. However, some patients may require an early operation in the case of joint complications such as femoro-tibial instability, or patella sub-dislocation, or if there is an increased risk of mid-term or long-term consequences for the joints (for instance, early arthrosis).

Surgical correction of leg bowing is a difficult task in patients affected with XLHR. The incidence of recurrence

is high, even in expert hands. In addition, complications such as spontaneous fusion of the pathological growth plate occur distant from the surgical site. Overall, the indication for surgical procedures in these patients should be considered bearing in mind the age of the child, metabolic control of the rickets, risk of long-term complications, risk of recurrence and potential iterative operations. Surgery before puberty should be avoided as it seems to be associated with a higher rate of recurrence. Our hope is that novel therapies such as antiFGF23 will prevent and/or heal the orthopedic complications encountered by XLHR children.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EC-17-0154>.

Declaration of interest

A Linglart has received honoraria and travel fees from Ultragenyx and Kyowakirin. A Rothenbuhler has received honoraria from Kyowakirin.

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Author contribution statement

The work described has not been published previously, and its publication is approved by all authors. All authors have made substantial contributions to the following: the conception and design of the study (A G, A L, P W), acquisition of data (A G, A R, Z P, G F, C G, B d B, A L, P W), analysis and interpretation of data (A G, A R, A L, P W) and drafting the article (A G, A L, P W), and all have given final approval of the version to be submitted (A G, A R, Z P, G F, C G, B d B, A L, P W).

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