Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH)

Rothenbuhler, Anya; Schnabel, Dirk; Högler, Wolfgang; Linglart, Agnes

DOI:
10.1016/j.metabol.2019.03.009

Document Version
Peer reviewed version

Citation for published version (Harvard):
Rothenbuhler, A, Schnabel, D, Högler, W & Linglart, A 2019, 'Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH)', *Metabolism*.
https://doi.org/10.1016/j.metabol.2019.03.009

Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH)

Anya Rothenbuhler[1, 2, 3]
Dirk Schnabel[4]
Wolfgang Högler[5, 6]
Agnes Linglart[1, 2, 3]

Affiliations

1 APHP, Endocrinology and Diabetology for Children, Bicêtre Paris Sud Hospital, Le Kremlin-Bicêtre, France
2 APHP, Reference Center for Rare Disorders of Calcium and Phosphate Metabolism, filière OSCAR, Paris, France
3 APHP, Platform of Expertise for Rare Disorders Paris-Sud, Bicêtre Paris Sud Hospital, Le Kremlin-Bicêtre, France
4 Center for Chronic Sick Children, Pediatric Endocrinology, Charité, University Medicine Berlin, Germany
5 Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom
6 Department of Pediatrics and Adolescent Medicine, Johannes Kepler University Linz, Linz, Austria

Corresponding author
Anya Rothenbuhler
Endocrinology and Diabetology for Children
Bicêtre Paris Sud Hospital, Le Kremlin-Bicêtre, France
anya.rothenbuhler@aphp.fr

Abstract

Early diagnosis, optimal therapeutic management and regular follow up of children with X-linked hypophosphatemia (XLH) determine their long term outcomes and future quality of life. Biochemical screening of potentially affected newborns in familial cases and improving physician's knowledge on clinical signs, symptoms and biochemical characteristics of XLH for *de novo* cases should lead to earlier diagnosis and treatment initiation. The follow-up of children with XLH includes clinical, biochemical and radiological monitoring of treatment (efficacy and complications) and screening for XLH-related dental, neurosurgical, rheumatological, cardiovascular, renal and ENT complications. In 2018, the European Union approved the use of burosumab, a humanized monoclonal anti-FGF23 antibody, as an alternative therapy to conventional therapy (active vitamin D analogues and phosphate supplements) in growing children with XLH and insufficiently controlled disease.

Diagnostic criteria of XLH and the principles of disease management with conventional treatment or with burosumab are reviewed in this paper.

Keywords

X-linked hypophosphatemia (XLH), alfacalcidol, burosumab, osteomalacia, rickets

1. INTRODUCTION

X-linked hypophosphatemic rickets (XLHR, OMIM 307800), a rare genetic disease due to inactivating mutations in the *PHEX* gene (Phosphate Regulating Gene with Homologies to the Endopeptidase on the X chromosome MIM #300550) is the most common form of hypophosphatemic rickets with an incidence of 1:20000(1,2).

PHEX is expressed in osteocytes and odontoblasts and inactivating *PHEX* mutations result in increased synthesis and secretion of fibroblast growth factor 23 (FGF23). Part of the pathophysiological mechanism that underlies XLHR is impaired proximal renal phosphate reabsorption and reduced 1-α–hydroxylation of 25-OH vitamin D due to the excess action of FGF23(3,4).

Children affected by XLH present with rickets, severely impaired mineralization of bone (osteomalacia) and teeth, and other signs and symptoms ultimately caused by excess FGF23, with the typical biochemical profile of hypophosphatemia, renal phosphate wasting and reduced calcitriol [1,25$(OH)_2$ vitamin D] concentration.

Early diagnosis and optimal management and follow-up of children and adolescents with XLH are the keys to successful outcomes, which determine the future quality of life of these patients. To date, large-scale natural history studies of XLH are lacking, which makes it is difficult to distinguish possibly inevitable long-term complications due to the underlying condition from sequelae of inadequate management. The burden of disease observed in today's adult XLH patients(5,6) suggests that late diagnosis and inadequate management contribute to adverse outcomes.

The aim of this review is to highlight the need for early diagnosis and optimal management so that children with XLH become healthier future adults.

2. DIAGNOSIS OF XLH

Disease awareness of physicians and affected family members leads to early diagnosis and thus early treatment initiation. Early diagnosis of XLH is of major importance since early treatment initiation leads to better outcomes such as improved linear growth and final height, bone mass accrual, fewer bone deformations and better dental health(7–11).

Two diagnostic settings need to be distinguished.

2.1 Diagnosis of familial cases of XLH

About 85-90% of familial cases of hypophosphatemic rickets are associated with *PHEX* gene mutations(10,12–19). XLH due to *PHEX* mutations follows an X-linked dominant inheritance pattern(2). Thus, affected fathers transmit the disease to all of their daughters and none of their sons. Affected mothers have a 50% risk of having an affected daughter or son. In the setting of familial XLH, potentially affected newborns should be biochemically screened and treatment should be initiated as soon as the diagnosis is made in order to prevent rachitic changes, leg bowing and short stature. If appropriately managed, it is unlikely that these patients develop active rickets and consequent orthopedic complications (figure 1).

However, even in familial XLH cases diagnosis can be delayed. Unfortunately, adult patients are often lost to follow-up and may not have been informed or may have incompletely understood the inheritance pattern. This is illustrated by the median age at diagnosis of XLH in familial cases of 1.3 years, ranging from 0.1 to 14.3 years (n=58; unpublished data obtained from patients followed at the French reference center of Bicêtre, Paris, and(20)). During the transition from pediatric to adult care, it is crucial to explain the inheritance pattern to adolescents and young adults with childbearing potential.

In babies born to parents affected with XLH, biochemical screening should be performed as soon as possible after the 1st week of life or certainly at first presentation to their family doctor. Screening includes serum phosphate, creatinine and alkaline phosphatase (ALP), and urinary phosphate and creatinine. Diagnosis of XLH is suspected if the serum phosphate level is below the normal range for newborns and if renal phosphate wasting is documented using the calculated renal phosphate reabsorption rate(21–23). It is essential that serum phosphate

and ALP concentrations are interpreted based on reference ranges for newborns and infants as these are physiologically higher than those for adults(24,25). Although clinical and radiological signs of rickets (figure 1) are often lacking in those babies, ALP may be found at the upper level of normal. Once diagnosis is made, the patient needs to be referred to a pediatrician specialized in bone disease (e.g. a pediatric endocrinologist) and treatment should be initiated immediately. The genetic diagnosis, i.e. *PHEX* sequencing, confirms the diagnosis; it may be done on cord blood or on a sample drawn after birth. Waiting for genetic results should not delay the start of treatment. Of note, a serum phosphate level within the normal range during the first months of life does not rule out the diagnosis and, in the absence of genetic diagnosis, the biochemical screening should be repeated including serum phosphate and ALP.

2.2 Diagnosis of *de novo* cases of XLH

Children with XLH due to *de novo PHEX* mutations, i.e. one third of the patients, are usually diagnosed after a diagnostic odyssey. Mean age at diagnosis is 3.9 ± 3.1 years, ranging from 0.9 to 13.1 years (unpublished data, Bicêtre, Paris) (figure 2a).

2.2.1 Revealing symptoms

Diverse clinical presentations may lead to the diagnosis of XLH. The most frequent and typical presentation is rickets (figure 1) which manifests as long bone deformities, especially leg bowing, delayed walking, waddling gait and bone/joint pain developing progressively once toddlers start standing and walking. In those patients, pediatricians and/or orthopedic surgeons are often the first specialists that are consulted because of leg deformities. As a certain degree of leg bowing in toddlers is considered physiological (26) (figure 2b), the first consultation may not always lead to a diagnostic work-up and therefore diagnosis is delayed until symptoms worsen. Stunted growth may be the revealing symptom in *de novo* XLH children (14% of cases in Bicêtre center; unpublished data); noteworthy, growth velocity is always poor at the time of diagnosis in those children. Rarely, the diagnosis of rickets is made from radiographs taken for other reasons, e.g. systematic screening of hip dysplasia in France.

2.2.2 Diagnostic criteria

Any leg bowing (*genu varum* or *valgum*) whether or not associated with poor statural growth, and widening of the metaphysis (ankles and wrists) should lead to a radiological and biochemical work-up. Tooth abscesses or facial cellulitis occurring on apparently healthy teeth suggest poor dentin mineralization(9). Radiological signs of XLH are detailed in this issue by C. Adamsbaum and colleagues. Briefly, radiographs of the hand, knees and lower limbs show the long bone deformities, abnormal growth plates with widened and frayed metaphyses. In contrast to other forms of rickets, bone cortices appear dense(20,27). At the time of diagnosis, fractures are uncommon in children and adolescents. Biochemical criteria (table 1) for the diagnosis of XLH include:

- serum phosphate below the normal threshold for age(28,29) associated with renal phosphate wasting, e.g. reduced calculated maximal tubular reabsorption of phosphate as a function of glomerular filtration rate (TmP/GFR)(21). Of note, the fractional tubular resorption of phosphate (TRP) value may be within the normal range in children with XLH, and in the presence of hypophosphatemia only the TmP/GFR is diagnostic;
- ALP levels above the upper limit of normal for age, indicating rickets/osteomalacia. In children, the measure of total ALP is used, in contrast to adults, in whom bone ALP should be measured preferably(20,30). Although ALP levels are elevated in XLH children and adolescents, the increase is not in the order of magnitude as seen in vitamin D deficiency rickets, defects in calcitriol synthesis or calcitriol receptor mutations (commonly called the vitamin D receptor) (figure 2c);
- parathyroid hormone (PTH) levels in the normal or upper normal range; any mild increase in PTH may be caused by underlying additional vitamin D or dietary calcium deficiency;
- normal serum calcium, and low urinary calcium excretion;
- exclusion of other proximal or distal tubular wasting disorders;
- exclusion, and otherwise prior correction, of vitamin D or dietary calcium deficiency.

In summary, the key to correct diagnosis of *de novo* XLH cases is good knowledge of the clinical signs and symptoms and the correct use of age-adjusted biochemical investigations to distinguish various forms of rickets.

The diagnosis of XLH may be confirmed by the measurement of elevated levels of intact FGF23. However, FGF23 concentrations may be inappropriately normal and this does not exclude the diagnosis. Patients with XLH produce levels of FGF23 that are well below those of patients with oncogenic osteomalacia (31,32). FGF23 levels are influenced by several factors including phosphate intake(33,34).

2.3 Genetic confirmation of XLH

The final confirmation of XLH is obtained through genetic analysis which identifies mutations in the *PHEX* gene in ~70% of patients with hypophosphatemic rickets, and 85-90% of patients when the disease is familial (2,12,16,19,35–46). Whenever possible, genetic analysis is recommended. Different types of *PHEX* mutations exist including point mutations, splice-site mutations, small and large deletions, deletions of pseudo-exons, and mosaicism, suggesting that several techniques or strategies may be necessary to reach a final diagnosis(18,39,47–51).

3. SEVERITY OF DISEASE AND COMPLICATIONS

We now have enough evidence to inform patients that XLH is a multisystemic disorder that may be associated with several complications including

- tooth abscesses, taurodontism (enlarged pulp chambers and body of tooth), facial cellulitis and periodontitis(52,53);
- premature fusion of cranial sutures leading to dolichocephaly and/or craniosynostosis; in some cases, patients may present with increased intracranial pressure, Chiari 1 malformation, syringomyelia, papillary oedema or neurological signs(54–61) ;
- hearing impairment(20,62–65);
- short stature: final height below -2SD is found in ~50% of patients adequately treated by conventional therapy(10,11,20,24,66–74);
- reduced muscle function due to hypophosphatemia(75,76);
- joint and bone pain

At the time of diagnosis, XLH children should undergo a thorough work-up to assess the severity/extent of the disease(20,30) including:

- measuring rickets severity, judged by inter-malleolar and intercondylar distances, 6MWT (6-minute walking test) as a global dynamic measure, serum ALP and PTH levels, serum and urinary calcium and phosphate concentrations, and hand, standing long leg and/or knee X-rays;
- assessing possible complications of the disease, i.e. craniosynostosis and its neurological complications(55,60), hearing impairment(62), abnormal dental mineralization(9), growth retardation(69), and reduced muscle function(76);
- measuring renal function (glomerular and tubular) and morphology before the start of therapy through kidney ultrasound and detailed biochemical work-up.

4. DIFFERENTIAL DIAGNOSIS

Once the diagnosis of rickets is confirmed by clinical, biochemical and radiological criteria, and the diagnosis of nutritional rickets and vitamin D resistant rickets (VDDR1-3), all of which are associated with secondary phosphate wasting due to high PTH levels, have been ruled out, other causes of hypophosphatemic rickets should be considered in patients who do not carry a *PHEX* variant, even if they display an elevated FGF23 level. The different causes of hypophosphatemic rickets are described in table 3.

Several rickets-like diseases that may lead to progressive bone deformities, abnormal gait and metaphyseal irregularities need to be excluded. These conditions may be found in the presence of low ALP levels, e.g. hypophosphatasia(77) or normal levels of ALP, e.g. healed nutritional rickets, Blount's disease or Schmid type metaphyseal dysplasia(78).

5. DISEASE MANAGEMENT

5.1 Principles of disease management

Once the diagnosis of XLH is established, the objective of the treatment is to restore the lower limb biomechanic axis and gait, improve growth, bone and teeth mineralization and muscular function. Disease management should also include social aspects, patient/family education and support. In addition, during follow up, the multidisciplinary team will aim at preventing the development of endocrine, orthopedic, rheumatologic,

metabolic, cardiovascular and renal complications. So far, international recommendations that could guide physicians in the management of these rare patients are lacking. However, some reports have been published including extensive physicians' expertise(20,30).

The patient pathway will involve different health and social disciplines throughout infancy, childhood and adolescence. We suggest that patients are seen at regular intervals by multidisciplinary teams lead by a pediatric expert in bone diseases, who will liaise with the patient's local healthcare providers (general practitioners/ pediatricians), a pediatric radiologist, orthopedic surgeon, physiotherapist, dentist and orthodontist. Additional professions may be required, e.g. pediatric neurosurgeon, ear, nose and throat (ENT) specialist, ophthalmologist, dietician, social worker and psychologist.

Two different therapies are currently available for XLH: active vitamin D analogues combined with phosphate supplements, and burosumab, the monoclonal fully human anti-FGF23 antibody. These treatments have different therapeutic objectives and outcomes, and therefore require different management as highlighted in table 2.

5.2 Conventional treatment with vitamin D analogues and phosphate supplements

For decades, the association of active vitamin D analogues (alfacalcidol or calcitriol) and phosphate supplements using multiple daily dosing was the only treatment option for children with XLH. The objective of this therapy is to counteract the calcitriol deficiency secondary to FGF23 exces and to compensate renal phosphate wasting. Medication doses reported in the literature, most of which date back over 20 years, vary widely, from 10-80 ng/kg/day of calcitriol and 30-180 mg/kg/day of elemental phosphate(8,20,67,79–83). Advice on treatment, based on recent reviews(20,30) and the authors' expertise is shown in table 2.

This therapy has demonstrated its efficacy to:

- decrease ALP concentrations to the upper limit of normal in ~ one year(20);
- improve bone deformity, bone pain and gait in 30 to 60% of patients(11,66,67,80,82,84–86);
- improve growth velocity in the magnitude of ~ 1 standard deviation(8,10,11,20,66–72,79,84,87);

- significantly improve dentin mineralization and therefore decrease teeth abscesses and oral complications in affected children(7,9,20,88,89).

Improvement in some of these outcomes, i.e. linear growth, final height, radiological features of rickets and oral health(7,10,11,90), has been associated with early treatment initiation and longer duration of treatment.

Many limitations to this therapy have been identified over the years and should be known by the caring physician, including:

- the absence of correction of the phosphate wasting with continued hypophosphatemia(20,30,80,85);
- the risk of nephrocalcinosis and/or urolithiasis; large doses of active vitamin D and oral phosphate supplements have both been associated with an increased rate of nephrocalcinosis in children(67,91–95);
- the risk of hyperparathyroidism; large oral doses of phosphate supplements are associated with the development of secondary and tertiary hyperparathyroidism by yet unknown mechanisms (8,86,91,92,96–100)
- the insufficient, or lack of, response of some children, leading to corrective surgeries of lower limbs(101);
- and the incomplete correction of muscle function deficits(75,76).

In addition to these major issues, we are lacking large scale studies to evaluate the impact of this conventional therapy on the quality of life and on the development of several disease complications such as craniosynostosis and hearing problems, enthesopathy, chronic pain and fatigue.

Dose Adjustment for conventional therapy (table 2)

The daily dose of phosphate supplements and vitamin D analogues is adjusted to serum ALP and PTH and urinary calcium/creatinine concentrations, clinical measures (leg bowing, growth velocity) and the patient's weight. The goal is to maintain normal ALP, PTH and urinary calcium/creatinine levels but not to normalise serum phosphate levels. During the first months of treatment, consistently elevated ALP levels without hypercalciuria should lead to an increase in active vitamin D analogue and/or phosphate dose. *Vice versa*, normalized ALP in the presence of hypercalciuria may require a reduction in the dose of active vitamin D analogues. If PTH level increases, one must consider lowering phosphate supplementation and/or increasing the dose of active vitamin D analogues. In all cases, strict adherence to medication, in particular the multiple daily dosing of phosphate is essential.

5.3 Novel therapy with anti-FGF23 antibody

As for today, the alternative therapy is burosumab, the humanized monoclonal anti-FGF23 antibody which was recently approved in the European Union for the treatment of XLH children over 1 year of age and adolescents who are still growing, and in the US for the treatment of all patients affected by XLH over 1 year of age(102,103). The main objective of this treatment is to counteract excess FGF23, thereby restoring phosphate reabsorption and endogenous $1,25(OH)_2$ vitamin D synthesis.

In children with severe XLH aged 5 to 12 years, the treatment with burosumab, given subcutaneously every 2 weeks was found to result in(104):

- a steady increase in serum phosphate concentration to a range between 1.1 and 1.6 mmol/l due to an increase in TmP/GFR;
- an increase in the calcitriol levels;
- an improvement in the radiographic rickets severity scores after 40 and 64 weeks of treatment;
- an improvement of physical function as shown by the increase in the distance walked during the 6MWT.

In contrast to conventional therapy, the burosumab dose is adjusted to the serum phosphate concentration as described in table 2. The recommended starting dose in Europe is 0.4 mg/kg body weight (0.8 mg/kg in US), followed by a titration period to reach a serum phosphate level in the low normal range for age, through dose increments every 4 weeks (maximum dose 2.0 mg/kg body weight or 90 mg every 15 days).

The limitations known to this treatment are(104–106):

- injections site reactions, headache and muscular pain;
- gain in growth velocity appears limited;
- the therapy is recent and therefore data on any long-term outcomes, e.g. hyperparathyroidism, nephrocalcinosis, surgery, body disproportion and adult complications such as enthesopathy are not yet available.

Given the available evidence for both therapies, we propose that children born into families affected with XLH, as well as children with a *de novo* diagnosis of XLH, be started on conventional therapy except if the diagnosis was delayed for several years, thus rickets considered as severe. In our view, treatment with burosumab should be offered (unless of course injections are refused), preferably with rigorous documentation and follow-up, to XLH children aged 1 year or older and in adolescents with growing skeletons if:

- they have radiographic evidence of rickets;
- they are refractory to conventional therapy;
- they experience complications related to conventional therapy.

6. DISEASE FOLLOW-UP (table 2)

Adequate follow-up of XLH patients includes clinical, biochemical and radiological monitoring of treatment (efficacy and complications) and screening for XLH-related dental, neurosurgical, rheumatological, cardiovascular, renal and/or ENT complications(20,30).

The parameters, as well as their frequency of assessment vary depending on age, disease severity and existing XLH-related complications.

6.1 Treatment monitoring

Clinical follow-up includes measuring intercondylar distance, intermalleolar distance, and if possible tibial torsion(107), height and growth velocity. An annual 6MWT can also be helpful in older children (from 5-6 years of age)(104,108). The number of dental abscesses and episodes of acute oral infections are recorded. The rachitic/osteomalacic, insufficiently treated bone, is associated with elevated ALP and low urinary calcium. In contrast, when rickets is healing, ALP tends to normalize, and urinary calcium to increase. The FGF23 level is not used as a tool for treatment monitoring in XLH children(33,109,110).

The efficacy and safety of conventional therapy, i.e. phosphate supplements and vitamin D analogues, is monitored by measuring ALP, the biomarker of rickets activity and osteomalacia(20,66,82,85). PTH is measured regularly as hyperparathyroidism is promoted by oral phosphate supplementation, especially during adolescence(8,86,91,111). Serum and specifically urine calcium measurements are necessary to evaluate the safety of vitamin D analogues. In children younger than 5 years of age, the 24 hours urine collection is quite difficult, and spot urine samples

are preferred. In children older than 5 years of age, 24 hours urine collections are advised if the urinary calcium is above the upper limit of normal (Uca/cr > 0.7 mmol/mmol)(112).

The follow-up of children with rickets may include radiographs. Once the diagnosis is made, radiological techniques using small amounts of X-rays, such as EOS, may be used whenever possible. Radiographs of lower limbs or knees (done not more than every 2 years) may be useful during follow-up. Radiographs may be indicated if patients are refractory to therapy, if orthopedic surgery is indicated, in cases of unexplained bone pain and before transition to adult care.

After initial treatment initiation and during physiological periods of rapid growth (infancy and puberty) it is useful to evaluate the patient every three months clinically and biochemically. This is also the case for patients of all ages with unsatisfactory results, e.g. ALP remaining high, worsening of leg bowing, or pain. Otherwise 6-monthly evaluation is sufficient.

The questions that should be asked if treatment objectives under conventional therapy are not achieved are:

Is treatment correctly prescribed?

- Are the doses appropriate? Adjusted to weight and growth velocity? Adjusted to biochemical markers?
- Are phosphate supplements prescribed in multiple daily doses?
- Is treatment correctly given? Are phosphate supplements given separately from calcium intakes such as milk and yogurt?
- Is compliance correct? As in many chronic diseases that require multiple daily doses of medication, poor compliance often explains poor metabolic control and poor clinical outcome.

6.2 Particular aspects concerning patients treated with burosumab

In patients treated with burosumab, serum phosphate is a strong biomarker of efficacy and is monitored for treatment titration and follow-up. In clinical trials, the phosphate target ranges from 1.1 to 1.6 mmol/l. Measurements are performed every 2 later every 4 weeks (104) for dose adjustment. We do not yet know the optimal serum phosphate target for children. During treatment, TmP/GFR and ALP require monitoring since they act as short-term and long-term biochemical markers of burosumab efficacy, respectively(104). The $1,25(OH)_2$ vitamin D

concentration increases rapidly upon burosumab therapy during 64 weeks of observation ; its value as a biomarker to adjust the therapy has not been evaluated(105,113,114).

7. SCREENING FOR XLH COMPLICATIONS

Craniosynostosis and premature fusion of cranial sutures are complications of XLH. Craniosynostosis should be screened for by assessing head circumference, skull shape and also neurological signs (fundoscopy, headaches). To date, there are no clear guidelines regarding MRI evaluations of children with XLH. However, recent data demonstrated the high frequency of Chiari 1 malformation and syringomyelia in XLH children raising the question whether systematic evaluation of the brain through MRI during childhood is indicated (55,60,115). In case of neurological symptoms, a CT scan and/or brain MRI should be done.

Hearing should be evaluated by audiometry during childhood; however data to identify the best time period or at risk patients is scarce(62).

Dental examination should be performed at least once a year in children(9). For details refer to the dedicated article on dental issues.

Growth should be monitored at least twice a year; bone age evaluation may be included in short children or in case of decreased growth velocity, a sign of active rickets which may require an increase in therapy(10,11,20,41,68,69). Growth hormone (GH) is not a standard treatment or indication for children with XLH. Studies have shown that GH increases short-term linear growth in short XLH children before puberty(116–123). Data on only 5 patients treated until final height showed no significant gain(124).

Nephrocalcinosis and nephrolithiasis are screened for using kidney ultrasounds and should be done at the start of therapy and approximately every 1-2 years depending on the urinary excretion of calcium(125).

Cardiovascular screening. To date, cardiac complications of XLH, on conventional therapy, are not commonly reported. This is surprising given that FGF23 has long been known to be associated with cardiovascular risk and the development of pathological hypertrophy that can lead to congestive heart failure(126). Only very recently was left ventricular hypertrophy and hypertension described in a subset of XLH patients in a prospective clinical study(127). Given the sparse evidence, it is difficult to come up with firm recommendations. We have decided to recommend cardiac echography every 5 years until further evidence emerges. Regular cardiac ultrasound measurements were part of the safety features of the burosumab clinical trials with no evidence of complications. Given the limited long-term safety data, we feel that regular echocardiography is required until more evidence emerges.

8. SOCIAL AND PATIENT EDUCATION FOLLOW-UP

Education of patients and families is crucial at the time of diagnosis. Regular updates are necessary to assess and encourage adherence to treatments, provide service contacts and information about patients' association groups, inform patients of scientific discoveries, including new therapies, support school and professional achievement and provide adequate social support (e.g. XLHnetwork.com; (1); http://phosphatdiabetes.de).

9. PERSPECTIVES

XLH is a multisystemic disorder that may manifest in children only once they start standing and walking. Untreated, or insufficiently treated, the disease leads to severe handicaps including bone pain, bone deformities, dental complications with abscesses and missing teeth, and short stature. The current conventional therapy, based on phosphate supplements and vitamin D analogues allows improvement in bone deformities, growth velocity and bone and dentin mineralization. However, this treatment does not restore normal phosphate levels and many patients do not respond fully/adequately to this therapy. Burosumab counteracts FGF23 excess thus restores renal phosphate reabsorption in treated children and adolescents. These convincing results have led to the approval of burosumab by EMA and FDA for the use in Europe and the USA. However, long-term data are needed, especially on growth, renal calcium excretion, PTH secretion and bone disease overall. When children evolve through adolescence and then adulthood, complications of their disease such as hearing impairment, hyperparathyroidism, cardiovascular and renal complications, rheumatological issues and enthesopathy may occur. These complications, which may be modified by the disease's therapy, render difficult the decision to stop or pursue the daily conventional treatment through adulthood once growth is complete. Since osteomalacia will return after any of the two therapies is stopped, adult bone specialists will need to gather further long-term treatment data.

Contributors

AR and AL wrote the initial draft of the article.

All authors contributed equally in the construction and the revision of the article.

All authors read and approved the final manuscript.

Acknowledgements

Publication of this article was supported by Kyowa Kirin Pharma. The company did not take part in writing, editing and revision of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

AR and AL received honoraria and travel grants from Kiowa Kirin and Ultragenyx.

DS reports honoraria, consulting fees and non-financial support from Kyowa Kirin, outside the submitted work.

WH received honoraria, research and travel support from Kyowa Kirin and honoraria and consulting fees from Ultragenyx.

Figure 1: Radiographic features of rickets in XLH children

A. Radiographs of lower limbs in a baby girl with an affected XLH father carrying a *PHEX* mutation. The baby is also affected; there are almost no signs of rickets on radiographs at birth. Treatment was started on day 7 with alfacalcidol 1ug/day (27 ng/kg/d) and phosphate supplements (Phosphoneuros®) 80 mg, 4 times per day (60 mg/kg/d) given twenty minutes after breast feeding. On radiographs at age 2.5 years, there were no signs of rickets (mild features at year 1). **B.** Different features of rickets, highlighting the variability in XLH disease severity, at the time of diagnosis in three children diagnosed late with *de novo PHEX* mutations.

Figure 2: Diagnosis of XLH in children

A. Age at diagnosis in children affected with XLH; we selected only the *de novo* cases (n=36 out of 94). The cohort of patients is followed at the Bicêtre reference center, Paris, France (unpublished). The mean age (+/- SD) at diagnosis (dotted line) was 3.9 ± 3.1 yrs, the median was 2.7 yrs [min: 0.9 - max:13.7] yrs. Each bar represents a case. **B.** Physiological distance between knees and ankles in children, adapted from. The upper part of the graph represents the 2SD intercondylar distance (positive) and the lower part the 2 SD intermalleolar distance (negative) and the mean values are represented in the middle of the graph. **C.** Serum ALP concentrations in 21 children with XLH at the time of diagnosis compared with 7 children affected by a molecular defect in the calcitriol (VDR) receptor. Median and 5^{th} - 95^{th} percentile of ALP are given.

Table 1: Diagnostic work up for XLH and differential diagnosis of hypophosphatemia

	Newborn Familial	**Child Familial**	**Infant-Child De novo**
			Take family history of leg bowing in infancy, dental problems, chronic 'rheumatological' pain and short stature
Radiographs		Left hand and wrist Standing lower limbs	Left hand and wrist (=bone age) Standing lower limbs
Blood biochemistry	Phosphate, calcium ALP Creatinine PTH	Phosphate, calcium ALP Creatinine PTH	Phosphate, calcium ALP Creatinine PTH 25OHD; $1,25(OH)_2D$ Electrolytes, blood gas
Urine biochemistry	Phosphate Creatinine Calcium	Phosphate Creatinine Calcium	Phosphate Creatinine Calcium Electrolytes Protein, aminoacids
Confirmation	*PHEX* genetics	*PHEX* genetics	Intact FGF23 *PHEX* genetics

25OHD: 25-hydroxy vitamin D; $1,25(OH)_2D$: 1,25-di-hydroxy vitamin D (calcitriol)

384 **Table 2:** Treatment doses, objectives and monitoring in children affected with XLH

		Vitamin D analogs and phosphate supplements		**Burosumab**
		Newborns or before the development of clinical or radiological signs of rickets	Clinical or radiological signs of rickets	Children > 1 year
Treatment doses	Starting dose	Alfacalcidol: 25-40 ng/kg/day (0.8-1 ug/day) Phosphate: 40-60 mg/kg/day (4 to 5 intakes/day)	Alfacalcidol: 40-80 ng/kg/day (1-1.5 ug/day) Phosphate: 40-60 mg/kg/day (4 to 5 intakes/day)	0.4 mg/kg/15 days in Europe 0.8 mg/kg/15 days in USA
	Maintenance dose	Alfacalcidol: 25-40 ng/kg/day (1-2 ug/day) Phosphate: 30-60 mg/kg/day (3 to 5 intakes/ day)		~ 1 mg/kg of body weight every 15 days
Efficacy markers	Outcomes	Time to the objective		
	Normal serum phosphate	Non applicable		1-4 months
	Normal urinary excretion of phosphate (TRP, TmP/GFR)			
	Increase in 1,25 (OH)2D without hypercalcemia			
	ALP normalization	6-12 months		
	Improvement of lower limb deformities	3-4 years		Data not available
	6MWT	No data		Improvement at 12 months
	Increase in growth velocity	1 year		No data
	Improvement of radiological signs of rickets on radiographs of lower limbs (RGI-C)	No data		10 months

	Improvement of POSNA, PODCI	No data	10 months
Safety markers		Frequency of follow-up	
	Serum calcium	3-6 months	
	Urinary calcium		
	Serum PTH		
	Renal ultrasound	1-2 years	
	Cardiac ultrasound	Every 5 years	Every 2 years until more evidence available

TRP: fractional tubular reabsorption of phosphate
TmP/GFR: ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
ALP **:** alkaline phosphatase
6MWT **:** 6-minute walk test
RGI-C: radiographic global impression of change
POSNA: pediatric musculoskeletal functional health questionnaire
PODCI: pediatric outcomes data collection instrument

Table 3: Non-exhaustive list of the causes of rickets associated with renal phosphate wasting. *

Disorder (abbreviation)	OMIM	Gene/location	Urinary Calcium	FGF23
Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signaling				
X-linked hypophosphatemia (XLH)	#307800	PHEX/Xp22.1	Low Undetectable	Normal or moderately elevated
Autosomal dominant hypophosphatemic rickets (ADHR)	#193100)	FGF23/12p13.3	Low Undetectable	Elevated
Autosomal recessive hypophosphatemic rickets 1 (ARHR1)	#241520	DMP1/4q22.1	Low Undetectable	Normal or moderately elevated
Autosomal recessive hypophosphatemic rickets 2 (ARHR2)	#613312	ENPP1/6q23.2	Low Undetectable	Normal or moderately elevated
Hypophosphatemic rickets and hyperparathyroidism	#612089	KLOTHO/13q13.1	Low	Elevated
Osteoglophonic dysplasia (OD)	#166250	FGFR1/8p12	Low	Normal or moderately elevated
Fibrous dysplasia (FD) Tumor induced osteomalacia (TIO) Cutaneous skeletal hypophosphatemia syndrome (CSHS) also called Schimmelpenning-Feuerstein-Mims syndrome (SFM)	#174800 #163200	GNAS/20q13.3 RAS/1p13.2	Low Undetectable	Normal or moderately elevated
Rickets/osteomalacia due to primary renal tubular phosphate wasting				
Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)	#241530	SLC34A3/9q34.3	Normal or high	Low or undetectable
X-linked recessive hypophosphatemic rickets (XLR, Dent's disease, Lowe syndrome)	#300554 #309000	CLCN5/Xp11.23 OCRL1/Xq25-26	Normal or high	Varies
Renal Fanconi syndrome due to cystinosis	#219800	CTNS/17p13.2	High	Low
Hypophosphatemia and nephrocalcinosis (NPHLOP1) Fanconi reno-tubular syndrome 2 (FRTS2)	#612286 #613388	SLC34A1/5q35.3	Elevated	Low or undetectable
Iatrogenic proximal tubulopathy = drug induced Fanconi Syndrome (for instance cisplatin, ifosfamide, tenofovir, sodium valproate)			Varies	Variable

* excluding causes of rickets with secondary phosphate wasting due to high PTH levels such as nutritional rickets, and rickets due to vitamin D deficiency or resistance.

References

1. Tenenhouse HS. X-linked hypophosphataemia: a homologous disorder in humans and mice. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1999 Feb;14(2):333–41.

2. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. Nat Genet. 1995 Oct;11(2):130–6.

3. Liu S, Tang W, Zhou J, Stubbs JR, Luo Q, Pi M, et al. Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. J Am Soc Nephrol JASN. 2006 May;17(5):1305–15.

4. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A. 2001 May 22;98(11):6500–5.

5. Che H, Roux C, Etcheto A, Rothenbuhler A, Kamenicky P, Linglart A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. Eur J Endocrinol. 2016 Mar;174(3):325–33.

6. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, Brixen K, Brock-Jacobsen B, Poulsen MR, et al. Phenotype presentation of hypophosphatemic rickets in adults. Calcif Tissue Int. 2010 Aug;87(2):108–19.

7. Biosse Duplan M, Coyac BR, Bardet C, Zadikian C, Rothenbuhler A, Kamenicky P, et al. Phosphate and Vitamin D Prevent Periodontitis in X-Linked Hypophosphatemia. J Dent Res. 2017 Apr;96(4):388–95.

8. Rasmussen H, Pechet M, Anast C, Mazur A, Gertner J, Broadus AE. Long-term treatment of familial hypophosphatemic rickets with oral phosphate and 1 alpha-hydroxyvitamin D3. J Pediatr. 1981 Jul;99(1):16–25.

9. Chaussain-Miller C, Sinding C, Wolikow M, Lasfargues J-J, Godeau G, Garabédian M. Dental abnormalities in patients with familial hypophosphatemic vitamin D-resistant rickets: prevention by early treatment with 1-hydroxyvitamin D. J Pediatr. 2003 Mar;142(3):324–31.
10. Quinlan C, Guegan K, Offiah A, Neill RO, Hiorns MP, Ellard S, et al. Growth in PHEX-associated X-linked hypophosphatemic rickets: the importance of early treatment. Pediatr Nephrol Berl Ger. 2012 Apr;27(4):581–8.
11. Mäkitie O, Doria A, Kooh SW, Cole WG, Daneman A, Sochett E. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. J Clin Endocrinol Metab. 2003 Aug;88(8):3591–7.
12. Gaucher C, Walrant-Debray O, Nguyen TM, Esterle L, Garabedian M, Jehan F. PHEX analysis in 118 pedigrees reveals new genetic clues in hypophosphatemic rickets. Hum Genet. 2009 May;125(4):401–11.
13. Holm IA, Nelson AE, Robinson BG, Mason RS, Marsh DJ, Cowell CT, et al. Mutational analysis and genotype-phenotype correlation of the PHEX gene in X-linked hypophosphatemic rickets. J Clin Endocrinol Metab. 2001 Aug;86(8):3889–99.
14. Li S-S, Gu J-M, Yu W-J, He J-W, Fu W-Z, Zhang Z-L. Seven novel and six de novo PHEX gene mutations in patients with hypophosphatemic rickets. Int J Mol Med. 2016 Dec 1;38(6):1703–14.
15. Morey M, Castro-Feijóo L, Barreiro J, Cabanas P, Pombo M, Gil M, et al. Genetic diagnosis of X-linked dominant hypophosphatemic rickets in a cohort study: Tubular reabsorption of phosphate and 1,25(OH) 2 D serum levels are associated with PHEX mutation type. BMC Med Genet. 2011 Sep 8;12(1):116.
16. Ruppe MD, Brosnan PG, Au KS, Tran PX, Dominguez BW, Northrup H. Mutational analysis of PHEX, FGF23 and DMP1 in a cohort of patients with hypophosphatemic rickets. Clin Endocrinol (Oxf). 2011 Mar;74(3):312–8.
17. Beck-Nielsen SS, Brixen K, Gram J, Brusgaard K. Mutational analysis of PHEX, FGF23, DMP1, SLC34A3 and CLCN5 in patients with hypophosphatemic rickets. J Hum Genet. 2012 Jul;57(7):453–8.
18. Ma SL, Vega-Warner V, Gillies C, Sampson MG, Kher V, Sethi SK, et al. Whole Exome Sequencing Reveals Novel PHEX Splice Site Mutations in Patients with Hypophosphatemic Rickets. PloS One. 2015;10(6):e0130729.
19. Ichikawa S, Traxler EA, Estwick SA, Curry LR, Johnson ML, Sorenson AH, et al. Mutational survey of the PHEX gene in patients with X-linked hypophosphatemic rickets. Bone. 2008 Oct;43(4):663–6.
20. Linglart A, Biosse-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S, et al. Therapeutic management of

hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014;3(1):R13-30.
21. Brodehl J. Assessment and interpretation of the tubular threshold for phosphate in infants and children. Pediatr Nephrol Berl Ger. 1994 Oct;8(5):645.
22. Brodehl J, Krause A, Hoyer PF. Assessment of maximal tubular phosphate reabsorption: comparison of direct measurement with the nomogram of Bijvoet. Pediatr Nephrol Berl Ger. 1988 Apr;2(2):183–9.
23. Mian AN, Schwartz GJ. Measurement and Estimation of Glomerular Filtration Rate in Children. Adv Chronic Kidney Dis. 2017 Nov;24(6):348–56.
24. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. Pediatr Nephrol Berl Ger. 2013 Apr;28(4):595–603.
25. Turan S, Topcu B, Gökçe İ, Güran T, Atay Z, Omar A, et al. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. J Clin Res Pediatr Endocrinol. 2011;3(1):7–11.
26. Greene WB. Genu varum and genu valgum in children: differential diagnosis and guidelines for evaluation. Compr Ther. 1996 Jan;22(1):22–9.
27. Cheung M, Roschger P, Klaushofer K, Veilleux L-N, Roughley P, Glorieux FH, et al. Cortical and trabecular bone density in X-linked hypophosphatemic rickets. J Clin Endocrinol Metab. 2013 May;98(5):E954-961.
28. Clayton BE, Jenkins, P. Clinical tests and refernce ranges. In: Paediatric chemical pathology. Blackwell Scientific Publications. Oxford; 1960.
29. Greenberg BG, Winters RW, Graham JB. The normal range of serum inorganic phosphorus and its utility as a discriminant in the diagnosis of congenital hypophosphatemia. J Clin Endocrinol Metab. 1960 Mar;20:364–79.
30. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res Off J Am Soc Bone Miner Res. 2011 Jul;26(7):1381–8.
31. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med. 2003 Apr 24;348(17):1656–63.
32. Nagata Y, Imanishi Y, Ishii A, Kurajoh M, Motoyama K, Morioka T, et al. Evaluation of bone markers in hypophosphatemic

474 rickets/osteomalacia. Endocrine. 2011 Oct 1;40(2):315.
475 33. Endo I, Fukumoto S, Ozono K, Namba N, Tanaka H, Inoue D, et al. Clinical usefulness of measurement of fibroblast growth factor 23
476 (FGF23) in hypophosphatemic patients: proposal of diagnostic criteria using FGF23 measurement. Bone. 2008 Jun;42(6):1235–9.
477 34. Souberbielle J-C, Prié D, Piketty M-L, Rothenbuhler A, Delanaye P, Chanson P, et al. Evaluation of a New Fully Automated Assay for
478 Plasma Intact FGF23. Calcif Tissue Int. 2017;101(5):510–8.
479 35. Dixon PH, Christie PT, Wooding C, Trump D, Grieff M, Holm I, et al. Mutational analysis of PHEX gene in X-linked hypophosphatemia. J
480 Clin Endocrinol Metab. 1998 Oct;83(10):3615–23.
481 36. Tyynismaa H, Kaitila I, Näntö-Salonen K, Ala-Houhala M, Alitalo T. Identification of fifteen novel PHEX gene mutations in Finnish
482 patients with hypophosphatemic rickets. Hum Mutat. 2000 Apr;15(4):383–4.
483 37. Guven A, Al-Rijjal RA, BinEssa HA, Dogan D, Kor Y, Zou M, et al. Mutational analysis of PHEX, FGF23 and CLCN5 in patients with
484 hypophosphataemic rickets. Clin Endocrinol (Oxf). 2017 Jul;87(1):103–12.
485 38. Song HR, Park JW, Cho DY, Yang JH, Yoon HR, Jung SC. PHEX gene mutations and genotype-phenotype analysis of Korean patients
486 with hypophosphatemic rickets. J Korean Med Sci. 2007 Dec;22(6):981–6.
487 39. Sabbagh Y, Jones AO, Tenenhouse HS. PHEXdb, a locus-specific database for mutations causing X-linked hypophosphatemia. Hum
488 Mutat. 2000;16(1):1–6.
489 40. Razali NN, Hwu TT, Thilakavathy K. Phosphate homeostasis and genetic mutations of familial hypophosphatemic rickets. J Pediatr
490 Endocrinol Metab JPEM. 2015 Sep;28(9–10):1009–17.
491 41. Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of
492 genotypes, phenotypes, and treatment complications. Eur J Endocrinol. 2016 Feb;174(2):125–36.
493 42. Popowska E, Pronicka E, Sulek A, Jurkiewicz D, Rowe P, Rowinska E, et al. X-linked hypophosphatemia in Polish patients. 1. Mutations
494 in the PHEX gene. J Appl Genet. 2000;41.
495 43. Popowska E, Pronicka E, Sulek A, Jurkiewicz D, Rowinska E, Sykut-Cegielska J, et al. X-linked hypophosphatemia in Polish patients. 2.
496 Analysis of clinical features and genotype-phenotype correlation. J Appl Genet. 2001;42(1):73–88.
497 44. Clausmeyer S, Hesse V, Clemens PC, Engelbach M, Kreuzer M, Becker-Rose P, et al. Mutational analysis of the PHEX gene: novel

498 point mutations and detection of large deletions by MLPA in patients with X-linked hypophosphatemic rickets. Calcif Tissue Int. 2009
499 Sep;85(3):211–20.
500 45. Cho HY, Lee BH, Kang JH, Ha IS, Cheong HI, Choi Y. A clinical and molecular genetic study of hypophosphatemic rickets in children.
501 Pediatr Res. 2005 Aug;58(2):329–33.
502 46. Capelli S, Donghi V, Maruca K, Vezzoli G, Corbetta S, Brandi ML, et al. Clinical and molecular heterogeneity in a large series of patients
503 with hypophosphatemic rickets. Bone. 2015 Oct;79:143–9.
504 47. Saito T, Nishii Y, Yasuda T, Ito N, Suzuki H, Igarashi T, et al. Familial hypophosphatemic rickets caused by a large deletion in PHEX
505 gene. Eur J Endocrinol. 2009 Oct;161(4):647–51.
506 48. Pekkarinen T, Lorenz-Depiereux B, Lohman M, Mäkitie O. Unusually severe hypophosphatemic rickets caused by a novel and complex
507 re-arrangement of the PHEX gene. Am J Med Genet A. 2014 Nov;164A(11):2931–7.
508 49. Zou M, Buluş D, Al-Rijjal RA, Andıran N, BinEssa H, Kattan WE, et al. Hypophosphatemic rickets caused by a novel splice donor site
509 mutation and activation of two cryptic splice donor sites in the PHEX gene. J Pediatr Endocrinol Metab JPEM. 2015 Jan;28(1–2):211–6.
510 50. Goji K, Ozaki K, Sadewa AH, Nishio H, Matsuo M. Somatic and germline mosaicism for a mutation of the PHEX gene can lead to
511 genetic transmission of X-linked hypophosphatemic rickets that mimics an autosomal dominant trait. J Clin Endocrinol Metab. 2006
512 Feb;91(2):365–70.
513 51. Christie PT, Harding B, Nesbit MA, Whyte MP, Thakker RV. X-linked hypophosphatemia attributable to pseudoexons of the PHEX gene.
514 J Clin Endocrinol Metab. 2001 Aug;86(8):3840–4.
515 52. Schwartz S, Scriver CR, Reade TM, Shields ED. Oral findings in patients with autosomal dominant hypophosphatemic bone disease
516 and X-linked hypophosphatemia: further evidence that they are different diseases. Oral Surg Oral Med Oral Pathol. 1988 Sep;66(3):310–4.
517 53. Pereira CM, de Andrade CR, Vargas PA, Coletta RD, de Almeida OP, Lopes MA. Dental alterations associated with X-linked
518 hypophosphatemic rickets. J Endod. 2004 Apr;30(4):241–5.
519 54. Caldemeyer KS, Boaz JC, Wappner RS, Moran CC, Smith RR, Quets JP. Chiari I malformation: association with hypophosphatemic
520 rickets and MR imaging appearance. Radiology. 1995 Jun 1;195(3):733–8.
521 55. Rothenbuhler A, Fadel N, Debza Y, Bacchetta J, Diallo MT, Adamsbaum C, et al. High Incidence of Cranial Synostosis and Chiari I

522 Malformation in Children With X-Linked Hypophosphatemic Rickets (XLHR). J Bone Miner Res Off J Am Soc Bone Miner Res. 2019
523 Mar;34(3):490–6.
524 56. Watts L, Wordsworth P. Chiari malformation, syringomyelia and bulbar palsy in X linked hypophosphataemia. BMJ Case Rep. 2015 Nov
525 11;2015.
526 57. Glass LRD, Dagi TF, Dagi LR. Papilledema in the setting of x-linked hypophosphatemic rickets with craniosynostosis. Case Rep
527 Ophthalmol. 2011 Sep;2(3):376–81.
528 58. Jaszczuk P, Rogers GF, Guzman R, Proctor MR. X-linked hypophosphatemic rickets and sagittal craniosynostosis: three patients
529 requiring operative cranial expansion: case series and literature review. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg. 2016
530 May;32(5):887–91.
531 59. Murthy AS. X-linked hypophosphatemic rickets and craniosynostosis. J Craniofac Surg. 2009 Mar;20(2):439–42.
532 60. Vega RA, Opalak C, Harshbarger RJ, Fearon JA, Ritter AM, Collins JJ, et al. Hypophosphatemic rickets and craniosynostosis: a
533 multicenter case series. J Neurosurg Pediatr. 2016 Jun;17(6):694–700.
534 61. Willis FR, Beattie TJ. Craniosynostosis in X-linked hypophosphataemic rickets. J Paediatr Child Health. 1997 Feb;33(1):78–9.
535 62. Pantel G, Probst R, Podvinec M, Gurtler N. Hearing loss and fluctuating hearing levels in X-linked hypophosphataemic osteomalacia. J
536 Laryngol Otol. 2009 Jan;123(1):136–40.
537 63. Meister M, Johnson A, Popelka GR, Kim GS, Whyte MP. Audiologic findings in young patients with hypophosphatemic bone disease.
538 Ann Otol Rhinol Laryngol. 1986 Jul;95(4 Pt 1):415–20.
539 64. Fishman G, Miller-Hansen D, Jacobsen C, Singhal VK, Alon US. Hearing impairment in familial X-linked hypophosphatemic rickets. Eur
540 J Pediatr. 2004 Oct 1;163(10):622–3.
541 65. Davies M, Kane R, Valentine J. Impaired hearing in X-linked hypophosphataemic (vitamin-D-resistant) osteomalacia. Ann Intern Med.
542 1984 Feb;100(2):230–2.
543 66. Tsuru N, Chan JC, Chinchilli VM. Renal hypophosphatemic rickets. Growth and mineral metabolism after treatment with calcitriol (1,25-
544 dihydroxyvitamin D3) and phosphate supplementation. Am J Child. 1987 Jan;141(1):108–10.
545 67. Verge CF, Lam A, Simpson JM, Cowell CT, Howard NJ, Silink M. Effects of therapy in X-linked hypophosphatemic rickets. N Engl J

546 Med. 1991 Dec 26;325(26):1843–8.
547 68. Fuente R, Gil-Peña H, Claramunt-Taberner D, Hernández O, Fernández-Iglesias A, Alonso-Durán L, et al. X-linked hypophosphatemia
548 and growth. Rev Endocr Metab Disord. 2017;18(1):107–15.
549 69. Zivicnjak M, Schnabel D, Billing H, Staude H, Filler G, Querfeld U, et al. Age-related stature and linear body segments in children with X-
550 linked hypophosphatemic rickets. Pediatr Nephrol. 2011 Feb;26(2):223–31.
551 70. Seikaly MG, Browne RH, Baum M. The Effect of Phosphate Supplementation on Linear Growth in Children with X-Linked
552 Hypophosphatemia. Pediatrics. 1994 Oct 1;94(4):478–81.
553 71. Friedman NE, Lobaugh B, Drezner MK. Effects of calcitriol and phosphorus therapy on the growth of patients with X-linked
554 hypophosphatemia. J Clin Endocrinol Metab. 1993 Apr;76(4):839–44.
555 72. Ariceta G, Langman CB. Growth in X-linked hypophosphatemic rickets. Eur J Pediatr. 2007 Apr;166(4):303–9.
556 73. Evans GA, Arulanantham K, Gage JR. Primary hypophosphatemic rickets. Effect of oral phosphate and vitamin D on growth and
557 surgical treatment. J Bone Joint Surg Am. 1980 Oct;62(7):1130–8.
558 74. Steendijk R, Hauspie RC. The pattern of growth and growth retardation of patients with hypophosphataemic vitamin D-resistant rickets:
559 a longitudinal study. Eur J Pediatr. 1992 Jun;151(6):422–7.
560 75. Veilleux L-N, Cheung MS, Glorieux FH, Rauch F. The muscle-bone relationship in X-linked hypophosphatemic rickets. J Clin Endocrinol
561 Metab. 2013 May;98(5):E990-995.
562 76. Veilleux L-N, Cheung M, Ben Amor M, Rauch F. Abnormalities in muscle density and muscle function in hypophosphatemic rickets. J
563 Clin Endocrinol Metab. 2012 Aug;97(8):E1492-1498.
564 77. Whyte MP. Hypophosphatasia and the role of alkaline phosphatase in skeletal mineralization. Endocr Rev. 1994 Aug;15(4):439–61.
565 78. Bonaventure J, Chaminade F, Maroteaux P. Mutations in three subdomains of the carboxy-terminal region of collagen type X account
566 for most of the Schmid metaphyseal dysplasias. Hum Genet. 1995 Jul;96(1):58–64.
567 79. Petersen DJ, Boniface AM, Schranck FW, Rupich RC, Whyte MP. X-linked hypophosphatemic rickets: a study (with literature review) of
568 linear growth response to calcitriol and phosphate therapy. J Bone Min Res. 1992 Jun;7(6):583–97.
569 80. Glorieux FH, Marie PJ, Pettifor JM, Delvin EE. Bone Response to Phosphate Salts, Ergocalciferol, and Calcitriol in Hypophosphatemic

570 Vitamin D-Resistant Rickets. N Engl J Med. 1980;303(18):1023–31.
571 81. Harrell RM, Lyles KW, Harrelson JM, Friedman NE, Drezner MK. Healing of bone disease in X-linked hypophosphatemic
572 rickets/osteomalacia. Induction and maintenance with phosphorus and calcitriol. J Clin Invest. 1985 Jun;75(6):1858–68.
573 82. Chesney RW, Mazess RB, Rose P, Hamstra AJ, DeLuca HF, Breed AL. Long-Term Influence of Calcitriol (1,25-Dihydroxyvitamin D) and
574 Supplemental Phosphate in X-Linked Hypophosphatemic Rickets. Pediatrics. 1983;71(4):559–67.
575 83. Scriver CR, Reade T, Halal F, Costa T, Cole DE. Autosomal hypophosphataemic bone disease responds to 1,25-(OH)2D3. Arch Child.
576 1981 Mar;56(3):203–7.
577 84. Balsan S, Tieder M. Linear growth in patients with hypophosphatemic vitamin D-resistant rickets: influence of treatment regimen and
578 parental height. J Pediatr. 1990 Mar;116(3):365–71.
579 85. Costa T, Marie PJ, Scriver CR, Cole DE, Reade TM, Nogrady B, et al. X-linked hypophosphatemia: effect of calcitriol on renal handling
580 of phosphate, serum phosphate, and bone mineralization. J Clin Endocrinol Metab. 1981 Mar;52(3):463–72.
581 86. Makitie O, Kooh SW, Sochett E. Prolonged high-dose phosphate treatment: a risk factor for tertiary hyperparathyroidism in X-linked
582 hypophosphatemic rickets. Clin Endocrinol Oxf. 2003 Feb;58(2):163–8.
583 87. Sochett E, Doria AS, Henriques F, Kooh SW, Daneman A, Mäkitie O. Growth and metabolic control during puberty in girls with X-linked
584 hypophosphataemic rickets. Horm Res. 2004;61(5):252–6.
585 88. Lee B-N, Jung H-Y, Chang H-S, Hwang Y-C, Oh W-M. Dental management of patients with X-linked hypophosphatemia. Restor Dent
586 Endod. 2017 May;42(2):146–51.
587 89. Douyere D, Joseph C, Gaucher C, Chaussain C, Courson F. Familial hypophosphatemic vitamin D-resistant rickets--prevention of
588 spontaneous dental abscesses on primary teeth: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Apr;107(4):525–30.
589 90. Connor J, Olear EA, Insogna KL, Katz L, Baker S, Kaur R, et al. Conventional Therapy in Adults With X-Linked Hypophosphatemia:
590 Effects on Enthesopathy and Dental Disease. J Clin Endocrinol Metab. 2015 Oct;100(10):3625–32.
591 91. Alon U, Lovell HB, Donaldson DL. Nephrocalcinosis, Hyperparathyroidism, and Renal Failure in Familial Hypophosphatemic Rickets.
592 Clin Pediatr (Phila). 1992 Mar 1;31(3):180–3.
593 92. Nielsen LH, Rahbek ET, Beck-Nielsen SS, Christesen HT. Treatment of hypophosphataemic rickets in children remains a challenge.

Dan Med J. 2014 Jul;61(7):A4874.
93. Taylor A, Sherman NH, Norman ME. Nephrocalcinosis in X-linked hypophosphatemia: effect of treatment versus disease. Pediatr Nephrol. 1995 Apr;9(2):173–5.
94. Seikaly M, Browne R, Baum M. Nephrocalcinosis Is Associated With Renal Tubular Acidosis in Children With X-Linked Hypophosphatemia. Pediatrics. 1996 Jan 1;97(1):91–3.
95. Goodyer PR, Kronick JB, Jequier S, Reade TM, Scriver CR. Nephrocalcinosis and its relationship to treatment of hereditary rickets. J Pediatr. 1987 Nov;111(5):700–4.
96. Yavropoulou MP, Kotsa K, Gotzamani Psarrakou A, Papazisi A, Tranga T, Ventis S, et al. Cinacalcet in hyperparathyroidism secondary to X-linked hypophosphatemic rickets: case report and brief literature review. Horm Athens Greece. 2010 Sep;9(3):274–8.
97. McHenry CR, Mostafavi K, Murphy TA. Tertiary hyperparathyroidism attributable to long-term oral phosphate therapy. Endocr Pract. 2006 May 1;12(3):294–8.
98. Rivkees SA, el-Hajj-Fuleihan G, Brown EM, Crawford JD. Tertiary hyperparathyroidism during high phosphate therapy of familial hypophosphatemic rickets. J Clin Endocrinol Metab. 1992 Dec;75(6):1514–8.
99. Carpenter TO, Olear EA, Zhang JH, Ellis BK, Simpson CA, Cheng D, et al. Effect of Paricalcitol on Circulating Parathyroid Hormone in X-Linked Hypophosphatemia: A Randomized, Double-Blind, Placebo-Controlled Study. J Clin Endocrinol Metab. 2014 Sep;99(9):3103–11.
100. Alon US, Levy-Olomucki R, Moore WV, Stubbs J, Liu S, Quarles LD. Calcimimetics as an Adjuvant Treatment for Familial Hypophosphatemic Rickets. Clin J Am Soc Nephrol. 2008 Jan 5;3(3):658–64.
101. Horn A, Wright J, Bockenhauer D, Van't Hoff W, Eastwood DM. The orthopaedic management of lower limb deformity in hypophosphataemic rickets. J Child Orthop. 2017 Aug 1;11(4):298–305.
102. New medicine for rare bone disease | European Medicines Agency [Internet]. [cited 2018 Oct 4]. Available from: https://www.ema.europa.eu/en/news/new-medicine-rare-bone-disease
103. Commissioner O of the. Press Announcements - FDA approves first therapy for rare inherited form of rickets, x-linked hypophosphatemia [Internet]. [cited 2018 Oct 4]. Available from: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm604810.htm

104. Carpenter TO, Whyte MP, Imel EA, Boot AM, Högler W, Linglart A, et al. Burosumab Therapy in Children with X-Linked Hypophosphatemia. N Engl J Med. 2018 24;378(21):1987–98.
105. Carpenter TO, Imel EA, Ruppe MD, Weber TJ, Klausner MA, Wooddell MM, et al. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. J Clin Invest. 2014 Apr;124(4):1587–97.
106. Insogna KL, Briot K, Imel EA, Kamenický P, Ruppe MD, Portale AA, et al. A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis. J Bone Miner Res Off J Am Soc Bone Miner Res. 2018 Jun 26;
107. Yeo A, James K, Ramachandran M. Normal lower limb variants in children. BMJ. 2015 Jul 7;350:h3394.
108. Saraff V, Schneider J, Colleselli V, Ruepp M, Rauchenzauner M, Neururer S, et al. Sex-, age-, and height-specific reference curves for the 6-min walk test in healthy children and adolescents. Eur J Pediatr. 2015 Jun;174(6):837–40.
109. Imel EA, DiMeglio LA, Hui SL, Carpenter TO, Econs MJ. Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. J Clin Endocrinol Metab. 2010 Apr;95(4):1846–50.
110. Carpenter TO, Insogna KL, Zhang JH, Ellis B, Nieman S, Simpson C, et al. Circulating levels of soluble klotho and FGF23 in X-linked hypophosphatemia: circadian variance, effects of treatment, and relationship to parathyroid status. J Clin Endocrinol Metab. 2010 Nov;95(11):E352-357.
111. Schmitt CP, Mehls O. The enigma of hyperparathyroidism in hypophosphatemic rickets. Pediatr Nephrol Berl Ger. 2004 May;19(5):473–7.
112. Matos V, van Melle G, Boulat O, Markert M, Bachmann C, Guignard JP. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr. 1997 Aug;131(2):252–7.
113. Ruppe MD, Zhang X, Imel EA, Weber TJ, Klausner MA, Ito T, et al. Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia. Bone Rep. 2016 Dec;5:158–62.
114. Zhang X, Imel EA, Ruppe MD, Weber TJ, Klausner MA, Ito T, et al. Pharmacokinetics and pharmacodynamics of a human monoclonal anti-FGF23 antibody (KRN23) in the first multiple ascending-dose trial treating adults with X-linked hypophosphatemia. J Clin Pharmacol. 2016;56(2):176–85.

115. Currarino G. Sagittal synostosis in X-linked hypophosphatemic rickets and related diseases. Pediatr Radiol. 2007 Aug;37(8):805–12.
116. Haffner D, Nissel R, Wuhl E, Mehls O. Effects of growth hormone treatment on body proportions and final height among small children with X-linked hypophosphatemic rickets. Pediatrics. 2004 Jun;113(6):e593-6.
117. Živičnjak M, Schnabel D, Staude H, Even G, Marx M, Beetz R, et al. Three-Year Growth Hormone Treatment in Short Children with X-Linked Hypophosphatemic Rickets: Effects on Linear Growth and Body Disproportion. J Clin Endocrinol Metab. 2011 Dec 1;96(12):E2097–105.
118. Makitie O, Toiviainen-Salo S, Marttinen E, Kaitila I, Sochett E, Sipila I. Metabolic control and growth during exclusive growth hormone treatment in X-linked hypophosphatemic rickets. Horm Res. 2008;69(4):212–20.
119. Huiming Y, Chaomin W. Recombinant growth hormone therapy for X-linked hypophosphatemia in children. Cochrane Database Syst Rev. 2005;(1):CD004447.
120. Reusz GS, Miltenyi G, Stubnya G, Szabo A, Horvath C, Byrd DJ, et al. X-linked hypophosphatemia: effects of treatment with recombinant human growth hormone. Pediatr Nephrol. 1997 Oct;11(5):573–7.
121. Saggese G, Baroncelli GI, Bertelloni S, Perri G. Long-term growth hormone treatment in children with renal hypophosphatemic rickets: effects on growth, mineral metabolism, and bone density. J Pediatr. 1995 Sep;127(3):395–402.
122. Seikaly MG, Brown R, Baum M. The effect of recombinant human growth hormone in children with X-linked hypophosphatemia. Pediatrics. 1997 Nov;100(5):879–84.
123. Rothenbuhler A, Esterle L, Gueorguieva I, Salles J-P, Mignot B, Colle M, et al. Two-year recombinant human growth hormone (rhGH) treatment is more effective in pre-pubertal compared to pubertal short children with X-linked hypophosphatemic rickets (XLHR). Growth Horm IGF Res Off J Growth Horm Res Soc Int IGF Res Soc. 2017;36:11–5.
124. Meyerhoff N, Haffner D, Staude H, Wühl E, Marx M, Beetz R, et al. Effects of growth hormone treatment on adult height in severely short children with X-linked hypophosphatemic rickets. Pediatr Nephrol Berl Ger. 2018 Mar;33(3):447–56.
125. Keskin M, Savaş-Erdeve Ş, Sağsak E, Çetinkaya S, Aycan Z. Risk factors affecting the development of nephrocalcinosis, the most common complication of hypophosphatemic rickets. J Pediatr Endocrinol Metab JPEM. 2015 Nov 1;28(11–12):1333–7.
126. Vervloet M. Renal and extrarenal effects of fibroblast growth factor 23. Nat Rev Nephrol. 2019 Feb;15(2):109–20.
127. Hernández-Frías O, Gil-Peña H, Pérez-Roldán JM, González-Sanchez S, Ariceta G, Chocrón S, et al. Risk of cardiovascular

involvement in pediatric patients with X-linked hypophosphatemia. Pediatr Nephrol Berl Ger. 2019 Jan 4;