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DOI: 10.1016/j.metabol.2019.03.009
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Document Version
Peer reviewed version

Citation for published version (Harvard):
https://doi.org/10.1016/j.metabol.2019.03.009

Link to publication on Research at Birmingham portal

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Download date: 22. Feb. 2021
Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH)

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**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 \textit{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\(^1\),\(^2\).

\textit{PHEX} is expressed in osteocytes and odontoblasts and inactivating \textit{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-\(\alpha\)-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 \([1,25(OH)_{2} \text{vitamin D}]\) 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 excess 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 burosumb 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 burosumb 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 alfalcacidol 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 5th - 95th percentile of ALP are given.
**Table 1: Diagnostic work up for XLH and differential diagnosis of hypophosphatemia**

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<th>Child Familial</th>
<th>Infant-Child De novo</th>
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<td><strong>Radiographs</strong></td>
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<td>Take family history of leg bowing in infancy, dental problems, chronic ‘rheumatological’ pain and short stature</td>
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<td>Left hand and wrist</td>
<td>Standing lower limbs</td>
<td>Left hand and wrist (=bone age) Standing lower limbs</td>
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<td></td>
<td>Phosphate Creatinine Calcium</td>
<td>Phosphate Creatinine Calcium</td>
<td>Phosphate Creatinine Calcium</td>
</tr>
<tr>
<td><strong>Urine biochemistry</strong></td>
<td>Phosphate Creatinine Calcium</td>
<td>Phosphate Creatinine Calcium</td>
<td>Phosphate Creatinine Calcium</td>
</tr>
<tr>
<td></td>
<td>Phosphate Creatinine Calcium</td>
<td>Phosphate Creatinine Calcium</td>
<td>Phosphate Creatinine Calcium</td>
</tr>
<tr>
<td><strong>Confirmation</strong></td>
<td>PHEX genetics</td>
<td>PHEX genetics</td>
<td>Intact FGF23 PHEX genetics</td>
</tr>
</tbody>
</table>

25OHD: 25-hydroxy vitamin D; 1,25(OH)\(_2\)D: 1,25-di-hydroxy vitamin D (calcitriol)
<table>
<thead>
<tr>
<th>Treatment doses</th>
<th>Vitamin D analogs and phosphate supplements</th>
<th>Burosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns or before the development of clinical or radiological signs of rickets</td>
<td>Clinical or radiological signs of rickets</td>
<td>Children &gt; 1 year</td>
</tr>
<tr>
<td><strong>Starting dose</strong></td>
<td>Alfacalcidol: 25-40 ng/kg/day (0.8-1 ug/day) Phosphate: 40-60 mg/kg/day (4 to 5 intakes/day)</td>
<td>Alfacalcidol: 40-80 ng/kg/day (1-1.5 ug/day) Phosphate: 40-60 mg/kg/day (4 to 5 intakes/day)</td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
<td>Alfacalcidol: 25-40 ng/kg/day (1-2 ug/day) Phosphate: 30-60 mg/kg/day (3 to 5 intakes/ day)</td>
<td>~ 1 mg/kg of body weight every 15 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy markers</th>
<th>Outcomes</th>
<th>Time to the objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal serum phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal urinary excretion of phosphate (TRP, TmP/GFR)</td>
<td>Non applicable</td>
<td>1-4 months</td>
</tr>
<tr>
<td>Increase in 1,25 (OH)2D without hypercalceemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP normalization</td>
<td></td>
<td>6-12 months</td>
</tr>
<tr>
<td>Improvement of lower limb deformities</td>
<td>3-4 years</td>
<td>Data not available</td>
</tr>
<tr>
<td>6MWT</td>
<td>No data</td>
<td>Improvement at 12 months</td>
</tr>
<tr>
<td>Increase in growth velocity</td>
<td>1 year</td>
<td>No data</td>
</tr>
<tr>
<td>Improvement of radiological signs of rickets on radiographs of lower limbs (RGI-C)</td>
<td>No data</td>
<td>10 months</td>
</tr>
<tr>
<td>Improvement of POSNA, PODCI</td>
<td>No data</td>
<td>10 months</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety markers</th>
<th>Frequency of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Urinary calcium</td>
<td></td>
</tr>
<tr>
<td>Serum PTH</td>
<td></td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td>1-2 years</td>
</tr>
<tr>
<td>Cardiac ultrasound</td>
<td>Every 5 years</td>
</tr>
</tbody>
</table>

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. *

<table>
<thead>
<tr>
<th>Disorder (abbreviation)</th>
<th>OMIM</th>
<th>Gene/location</th>
<th>Urinary Calcium</th>
<th>FGF23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signaling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked hypophosphatemia (XLH)</td>
<td>#307800</td>
<td>PHEX/Xp22.1</td>
<td>Low Undetectable</td>
<td>Normal or moderately elevated</td>
</tr>
<tr>
<td>Autosomal dominant hypophosphatemic rickets (ADHR)</td>
<td>#193100</td>
<td>FGF23/12p13.3</td>
<td>Low Undetectable</td>
<td>Elevated</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets 1 (ARHR1)</td>
<td>#241520</td>
<td>DMP1/4q22.1</td>
<td>Low Undetectable</td>
<td>Normal or moderately elevated</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets 2 (ARHR2)</td>
<td>#613312</td>
<td>ENPP1/6q23.2</td>
<td>Low Undetectable</td>
<td>Normal or moderately elevated</td>
</tr>
<tr>
<td>Hypophosphatemic rickets and hyperparathyroidism</td>
<td>#612089</td>
<td>KLOTHO/13q13.1</td>
<td>Low</td>
<td>Elevated</td>
</tr>
<tr>
<td>Osteoglophonic dysplasia (OD)</td>
<td>#166250</td>
<td>FGFR1/8p12</td>
<td>Low</td>
<td>Normal or moderately elevated</td>
</tr>
<tr>
<td>Fibrous dysplasia (FD)</td>
<td>#174800</td>
<td>GNAS/20q13.3</td>
<td>Low</td>
<td>Normal or moderately elevated</td>
</tr>
<tr>
<td>Tumor induced osteomalacia (TIO)</td>
<td>#163200</td>
<td>RAS/1p13.2</td>
<td>Low Undetectable</td>
<td>Normal or moderately elevated</td>
</tr>
<tr>
<td>Cutaneous skeletal hypophosphatemia syndrome (CSHS) also called Schimmelpenning-Feuerstein-Mims syndrome (SFM)</td>
<td>#174800</td>
<td>GNAS/20q13.3</td>
<td>Low</td>
<td>Normal or moderately elevated</td>
</tr>
<tr>
<td>* Hypophosphatemic rickets and hyperparathyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rickets/osteomalacia due to primary renal tubular phosphate wasting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)</td>
<td>#241530</td>
<td>SLC34A3/9q34.3</td>
<td>Normal or high</td>
<td>Low or undetectable</td>
</tr>
<tr>
<td>X-linked recessive hypophosphatemic rickets (XLR, Dent’s disease, Lowe syndrome)</td>
<td>#300554</td>
<td>CLCN5/Xp11.23</td>
<td>Normal or high</td>
<td>Varies</td>
</tr>
<tr>
<td>#309000</td>
<td>OCLN1/Xq25-26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Fanconi syndrome due to cystinosis</td>
<td>#219800</td>
<td>CTNS/17p13.2</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Hypophosphatemia and nephrocalcinosis (NPHLOP1)</td>
<td>#612286</td>
<td>SLC34A1/5q35.3</td>
<td>Elevated</td>
<td>Low or undetectable</td>
</tr>
<tr>
<td>Fanconi reno-tubular syndrome 2 (FRTS2)</td>
<td>#613388</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iatrogenic proximal tubulopathy = drug induced Fanconi Syndrome (for instance cisplatin, ifosfamide, tenofovir, sodium valproate)</td>
<td></td>
<td></td>
<td>Varies</td>
<td>Variable</td>
</tr>
</tbody>
</table>
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.


20. Linglart A, Biosse-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S, et al. Therapeutic management of


