Clinical Reviews in Bone and Mineral Metabolism (2019) 17:138–141
https://doi.org/10.1007/s12018-019-09266-y

REVIEW PAPER

X-linked Hypophosphatemic Rickets: the Challenges of Treatment

Jessica Sammut[1,2] · Miriam Giordano Imbroll[1,2] · Mark Gruppetta[1,2]

Published online: 29 October 2019

Abstract
X-linked dominant hypophosphatemic rickets (XLHR) is the most common inherited form of rickets due to a mutation in the phosphate regulating gene with homologies to endopeptidases on the X chromosome (PHEX gene) expressed in bones and teeth. This leads to impaired renal reabsorption of phosphate and defective bone mineralization. Clinical presentation often occurs in childhood, where children mostly present with bow legs, delayed walking, or gait difficulties. Other clinical features may also be present and these are described in this review in addition to the classic laboratory findings. Focus is made on the management of XLHR and its challenges, highlighting the complications that may arise from medical treatment with reference to literature. Moreover, we also describe novel treatment in XLHR; the potential use of growth hormone and cinacalcet, and the newly approved human monoclonal antibody against FGF-23 as a more targeted therapy.

Keywords Rickets · Hypophosphatemic · X-linked · Bone · PHEX

Introduction

X-linked hypophosphatemic rickets (XLHR) is the most common inherited form of rickets characterized by defective bone mineralization in childhood with an estimated incidence of 1 in 20,000 worldwide [1]. It has X-linked dominant inheritance and is caused by a mutation in the phosphate regulating gene with homologies to endopeptidases on the X chromosome (*PHEX* gene) resulting in impaired renal reabsorption of phosphate [2]. Phosphorus is an essential mineral found as organic and inorganic phosphate in the body and it is mostly found bound to calcium to provide strength to bones and teeth. Hence, phosphate wasting can lead to abnormal bone development [1].

Pathophysiology of XLHR

The *PHEX* gene is expressed in bones and teeth during late embryonic development to initiate bone mineralization. Inactivating mutations in the *PHEX* gene such as missense and nonsense mutations result in XLHR. There are over 170 mutations described in literature [1] and these mutations cause increased concentrations of Fibroblast Growth Factor 23 (FGF-23) which reduce the expression of the sodium-phosphate cotransporters (NaPi-IIa, NaPi-IIc, Pit-2) on the apical surface of the proximal renal tubule cells and thus prevent phosphate reabsorption. The expression of NaPi-IIa and NaPi-IIc can also be modified by Parathyroid Hormone (PTH). High circulating levels of FGF-23 also impairs the hydroxylation of 1,25OH Vitamin D thus impairing both renal and intestinal phosphate absorption [3]. Through these mechanisms, both renal and digestive absorption of phosphate are diminished and this provides the underlying rationale in the management of XLHR.

Clinical Features & Laboratory Findings

Clinical presentation of XLHR often occurs in childhood, where children mostly present with bow legs, delayed walking, or gait difficulties. These are three characteristic features, although other clinical features include short stature, frontal bossing, flaring of the metaphysis, rachitic rosary, and dental abscesses [1]. Hearing impairment may also be a feature, and there can be premature fusion of the cranial sutures resulting in craniosynostosis and raised intracranial pressure [4]. In

✉ Jessica Sammut
jes.sammut@gmail.com

[1] Department of Medicine, Faculty of Medicine and Surgery, University of Malta, Mater Dei Hospital, Msida, Malta

[2] Diabetes and Endocrine Centre, Department of Medicine, Mater Dei Hospital, Msida, Malta

adulthood, patients may experience bone and joint pains as well as joint stiffness from enthesopathy and osteoarthritis [1]. Cardiovascular complications are rare, however, hypertension and left ventricular hypertrophy have been reported [5].

Classic laboratory findings of XLHR include low serum phosphate, normal serum calcium, low to normal circulating 1,25(OH) Vitamin D levels, normal circulating 25(OH) Vitamin D, high serum alkaline phosphatase (ALP), normal PTH, and reduced tubular absorption of phosphate corrected for glomerular filtration rate (TmP/GFR) [2]. Radiologically, the growth plates are widened with flaring and cupping of the metaphyses, mostly prominent in areas where growth is greatest including the distal femur and proximal tibia, the wrist, and the anterior rib ends [6]. However, molecular genetics is needed to confirm the diagnosis.

Management

Management of XLHR requires a multidisciplinary team approach in order to improve bone deformities, maximize growth and preserve dentition. In 2011, Carpenter et al. have issued recommendations on the management of XLHR and highlighted differences in the treatment between pediatric and adult patients [2].

In the pediatric population, the aim of early medical treatment is not to normalize the serum phosphate concentration but to help improve leg deformities in order to reduce future surgical corrections and improve adult height. Recommendations include activated Vitamin D in the form of Calcitriol or 1-alfacalcidol at a dose of 20–30 ng/kg/day in 2 to 3 divided doses, and phosphate supplementation of 20–40 mg/kg/day in 3 to 5 divided doses [2]. However, patients are usually started at lower doses and titrated upwards in order to avoid the gastrointestinal side effects that may limit compliance.

In adults, on the other hand, medical treatment should aim to reduce bone pain, to reduce the extent of osteomalacia and to improve fracture healing or surgical recovery. Carpenter et al. suggests that if no clinical improvement is reached within 9 to 12 months, treatment should probably be discontinued [2]. The recommended dose in adults was with 0.50–0.75 mg/day of calcitriol in two divided doses starting 1 week before the phosphate supplementation to reduce the risk of exacerbating pre-existing secondary hyperparathyroidism. The recommended dose of phosphate supplements in adults in 750–1000 mg/day in 3–4 divided doses.

Surgery is usually delayed until growth has nearly ceased as certain bone deformities may improve with pharmacological treatment alone. In certain cases, however, early surgery may be required if severe bowing or tibial torsion limits mobility [2].

Apart from medical and surgical management, patients should be offered physiotherapy to improve joint stability and muscle strength [7]. Regular dental check-ups as well as appropriate dental hygiene with brushing 2–3 times/daily should also be advised in order to prevent risk of dental abscesses [1].

Complications of Treatment

Treatment of XLHR is not without complications. Nephrocalcinosis can develop in 71% of cases which are treated with oral phosphate [8, 9] and this can progress to chronic kidney disease with a reduction in the glomerular filtration rate [2]. A study has also suggested that the type of *PHEX* mutation can be useful in predicting which patients are at increased risk of developing the condition [10].

High doses of phosphate supplementation can also cause decreased serum ionized calcium, stimulating the parathyroid glands and thus causing secondary hyperparathyroidism. Additionally, phosphate can increase PTH secretion and synthesis by post-transcriptional mechanism independent of serum calcium and calcitriol [11]. However, this stage is reversible with dose adjustment of phosphate supplementation. In cases where hyperparathyroidism persists, it can cause parathyroid hyperplasia and progress to tertiary hyperparathyroidism. Medical therapy is often ineffective at this stage and should be treated with parathyroidectomy [12]. In certain cases, hyperparathyroidism can also be seen in untreated patients thus indicating that the type of PHEX mutation can also play a role in developing this complication [10].

Hypertension and left ventricular hypertrophy have also been infrequently reported, however, there is not enough evidence on whether these complications are directly related to XLHR or a side-effect of conventional therapy [13]. Some have proposed that these cardiovascular complications may develop secondary to the development of hyperparathyroidism and nephrocalcinosis [5, 14]. FGF-23 may also have a role due to its effect on renal sodium absorption as well as causing cardiac myocyte hypertrophy [13].

Recognizing such complications early is essential for appropriate management and thus patients with XLHR should be monitored with laboratory investigations and imaging. Medical treatment should be adjusted according to serum ALP, PTH, and urinary calcium/creatinine with serum ALP serving as important marker of bone healing [2]. Table 1 summarizes the recommendations for XLHR monitoring.

Novel Treatment

Despite the recommended use of activated Vitamin D and phosphate supplementation for the treatment of XLHR, some

Table 1 Summary of the recommendations for XLHR monitoring [2] [4]

Recommendations for XLHR monitoring	
Laboratory monitoring (serum calcium, serum phosphate, serum creatinine, serum ALP, serum PTH, urinary calcium and creatinine)	Childhood: Three monthly intervals Adulthood: After 4–6 weeks of starting treatment, then every 6–8 weeks until stable for 1 year, then every 6–9 months
Radiographs	At diagnosis, then every 2 years for assessment of healing Others: To evaluate skeletal deformities for surgery To evaluate bone pain
Technetium bone scan	When suspecting stress fractures
US kidneys	Every 2–5 years
CT/MRI brain	Only if neurological symptoms
Audiometry	In childhood
Dental examination	Once a year
Growth monitoring (height, weight, head circumference, skull shape)	Twice a year
Cardiovascular screening (ECHO)	Every 5 years

studies have suggested the use of growth hormone (GH) therapy as an adjunct for XLHR. This is because GH and Insulin Growth Factor 1 (IGF-1) transiently increase phosphate reabsorption and possibly improve linear growth in patients with short stature [7]. However, worsening of leg deformities and radiological findings were also reported with GH therapy, and thus further research is needed to determine efficacy of such treatment [1, 2].

Cinacalcet, a calcimimetic agent which increases the sensitivity of the calcium-sensing receptor to extracellular calcium, can also be effective in reducing PTH in XLHR and prevent secondary hyperparathyroidism. It is already approved to reduce PTH in chronic kidney disease and hyperparathyroidism, however, further long-term randomized controlled trials are needed to identify its safety profile in XLHR [2].

With the recent advances in understanding the molecular pathogenesis of XLHR, neutralizing antibodies to FGF-23 have been developed as a more targeted therapy in patients with XLHR. In 2018, the European Medicines Agency has authorized the conditional approval of the human monoclonal antibody directed against FGF-23, Burosumab, for children over 1 year and growing adolescents who have radiological evidence of bone disease. In the USA, it is approved for all patients with XLHR over 1 year. It is given as a subcutaneous injection every 2 weeks [4]. Studies have shown that Burosumab increased serum phosphate, improved rickets severity and improved patient's level of physical function and growth in children of all ages [15–18].

Conclusion

Management of XLHR has always been a challenge in view of the complications associated with conventional treatment. The increased knowledge on the pathophysiology of XLHR, has provided more targeted therapy that until now has shown to be more effective with less complications. However, anti-FGF23 antibody treatment is expensive and thus conventional treatment with activated Vitamin D and phosphate supplements still remains the first-line treatment in patients with XLHR. Thus, monitoring with laboratory investigations and imaging remains essential to avoid and treat complications early and minimize the burden of the disease.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Lee JY, Imel EA. The changing face of hypophosphatemic disorders in the FGF-23 era. Pediatr Endocrinol Rev. 2013;10:367–79.
2. Carpenter T, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res. 2011;26:1381–8.
3. Fuente R, Gil-Peña H, Claramunt-Taberner D, Hernández O, Fernández-Iglesias A, Alonso-Durán L, et al. X-linked

hypophosphatemia and growth. Rev Endocr Metab Disord. 2017;18:107–15.
4. Rothenbuhler A, Schnabel D, Högler W, Linglart A. Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH). Metabolism. 2019. https://doi.org/10.1016/j.metabol.2019.03.009.
5. Nehgme R, Fahey JT, Smith C, Carpenter TO. Cardiovascular abnormalities in patients with X-linked hypophosphatemia. J Clin Endocrinol Metab. 1997;82:2450–4.
6. Cheema JI, Grissom LE, Harcke TH. Radiographic characteristics of lower-extremity bowing in children. Radiographics. 2003. https://doi.org/10.1148/rg.234025149.
7. 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:R13–30.
8. Taylor A, Sherman NH, Norman ME. Nephrocalcinosis in X-linked hypophosphatemia: effect of treatment versus disease. Pediatr Nephrol. 1995;9:173–5.
9. Quinlan C, Guegan K, Offiah A, O'Neill R, Hiorns MP, Ellard S, et al. Growth in PHEX-associated X-linked hypophosphatemic rickets: the importance of early treatment. Pediatr Nephrol. 2012;27:581–8.
10. 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)2D serum levels are associated with PHEX mutation type. BMC Med Genet. 2011;12:116.
11. Sarıakçalı B, Jamaspishvili E, Evran M, Sert M, Tetiker T. A case of hypophosphatemic rickets with the secondary hyperparathyroidism. Am J Med Case Rep. 2014;2:158–60.
12. Savio RM, Gosnell JE, Posen S, Reeve TS, Delbridge LW. Parathyroidectomy for tertiary hyperparathyroidism associated with X-linked dominant hypophosphatemic rickets. Arch Surg. 2004;139:218–22.
13. Beck-Nielsen SS, Mughal Z, Haffner D, Nilsson O, Levtchenko E, Ariceta G, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J Rare Dis. 2019;14:58.
14. Nakamura Y, Takagi M, Takeda R, Miyai K, Hasegawa Y. Hypertension is a characteristic complication of X-linked hypophosphatemia. Endocr J. 2017;64:283–9.
15. Whyte MP, Carpenter TO, Gottesman GS, Mao M, Skrinar A, San Martin J, et al. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. Lancet Diabetes Endocrinol. 2019;7:189–99.
16. Carpenter TO, Whyte MP, Imel EA, Boot AM, Högler W, Lingart A, et al. Burosumab therapy in children with X-linked hypophosphatemia. N Engl J Med. 2018;378:1987–98.
17. Imel EA, Glorieux FH, Whyte MP, Munns CF, Ward LM, Nilsson O, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet. 2019. https://doi.org/10.1016/S0140-6736(19)30654-3.
18. 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;124:1587–97.