Open Access
Journal of the Faculty of Medicine Baghdad
Print ISSN: 0041-9419, Online-ISSN: 2410-8057
DOI: *https://doi.org/10.32007/jfacmedbaghdad.6632349*
Review Article

A Review Article: Impact of Growth Hormone Treatment on Height in Children with X-Linked Hypophosphatemic Rickets

Munib A. Al-Zubaidi[1], Wasnaa H. Abdullah[2*]
[1] *Department of Pediatrics, College of Medicine, University of Baghdad, Baghdad, Iraq.*
[2] *Department of Pediatrics, College of Medicine, Mustansiriyah University, Baghdad, Iraq.*

Received: March 2024
Revised: Aug. 2024
Accepted: Aug 2024
Published: Oct .2024

Abstract

Background: X-linked hypophosphatemic rickets (XLHR) is the most frequent form of inherited rickets. In children, stunted growth and disproportionately short stature are frequently the early signs of XLHR.

Objective: To review different opinions in the review of literature about the use of growth hormone in the treatment of XLHR.

Methods: This review article followed a systematic literature review approach, there are no exclusion criteria.

Main Findings: Growth retardation may continue even after receiving appropriate conventional treatment (phosphate supplements and active analogs of vitamin D) in XLHR, even if it is initiated early in childhood. Recently, regardless of a well-controlled disease, treatment with recombinant human growth hormone (rhGH) was suggested as an effective way of supporting growth in children with XLHR exhibiting a lack of growth. It is necessary to follow until reaching adult height to assess the long-term effects of rhGH treatment on the ultimate height.

Conclusion: The addition of rhGH to optimal medical treatment might represent a promising option in the significant portion of affected patients with XLHR and growth failure. Follow-up is needed until the final height is reached to evaluate the long-term benefit of rhGH treatment on final height. Further studies will be necessary to determine the most efficient treatment protocol concerning doses, duration, and age of initiation or rhGH in short children with XLHR. However, further studies would be needed to study the addition of rhGH to optimal medical treatment in short children with XLHR.

Keywords: Growth hormone; Rickets; Short stature; X-linked dominant; X-linked hypophosphatemic.

Introduction

Definition: X-linked hypophosphatemic rickets (XLHR), is the most frequent form of inherited rickets affecting 3.9 - 5 / 100,000 live births (1). Genetics of XLHR: X-linked hypophosphatemic rickets is a hereditary disease caused by the loss of function mutations in the Phosphate phosphate-regulating endopeptidase X-Linked (*PHEX*) gene which is localized on Xp22.1. *PHEX* genes encode a particular endopeptidase which is highly displayed in the cells of the teeth (odontoblasts) and bones (osteocytes, osteoblasts) (2). Studies show that when PHEX function is lost, fibroblast growth factor 23 (FGF23) is secreted more readily; which can cause hypophosphatemia, urinary phosphate loss, and insufficient production of calcitriol (1, 25(OH) 2 Vitamin D) (3). Both heterozygous females and hemizygous males are affected by XLHR, which is inherited in an X-linked dominant pattern. Hemizygous males with a *PHEX* pathogenic variant pass it on to all of their daughters (who will be heterozygote affected) but not to any of their sons (non-affected). Male and Female progeny who inherit the pathogenic variant will be affected.

Corresponding author: wasnaa.hadi@uomustansiriyah.edu.iq

Affected females have a 50% chance of passing on the pathogenic mutation to each child. When a family member inherits a *PHEX* pathogenic variation,the degree of symptoms can vary; however, intrafamilial clinical variability is not related to the affected family member's sex. It is possible to do prenatal and preimplantation genetic testing for XLHR if a family member with the *PHEX* pathogenic variation has been discovered (1).

Clinical and biochemical features of XLHR: Hypophosphatemia can present in the neonatal period, alkaline phosphatase can be elevated at the first month of life, and an early treatment with high doses of vitamin D may not prevent growth failure. Patients with the X-linked disorder do not show muscle weakness, tetany, or hypocalcemia. Adults, especially males, with XLHR may develop progressive ankylosis of the spine and major joints, simulating ankylosing spondylitis (4). Clinically, children with XLHR are characterized by short stature, and progressive leg bowing that develops as toddlers begin to stand and walk associated with radiological features of rickets, in addition to dental abscesses (5).

Biochemically, XLHR can be identified by raised serum alkaline phosphatase levels, low 1.25 dihydroxy vitamin D3 levels (calcitriol), normal

serum calcium and 25-OH vitamin D3 levels, and most importantly is hypophosphatemia and phosphaturia due to inadequate renal tubular reabsorption of phosphate) (5,6).

Growth status in patients with XLHR: In children, stunted growth and disproportionately short stature are frequently the early signs of XLHR. The length at birth is stated to be normal in children with XLHR (1). However, during the first few years of life, growth retardation becomes noticeable (7), leading to a mean height that is of 2 standard deviation scores (SDS) or more below the reference population's mean height (2). Unfortunately, growth retardation may continue even after receiving appropriate traditional therapy (phosphate supplements and active analogs of vitamin D), even if it is initiated early in childhood. In fact, the majority of studies have shown that approximately 50% of treated XLHR children remain short (< − 2 SDS) when growth has finished, which leads to a poor final adult height (8). There is yet, no fully effective treatment for XLHR. Growth retardation and skeletal abnormalities in XLHR patients have been proven to improve with using calcitriol in addition to oral phosphate (9). However, compliance with this regimen over the long term is challenging, and for some patients, the treatment outcomes are unsatisfactory. Many patients never show signs of catch-up growth or attain normal stature, even with the most effective medical therapy possible (10). Cohorts of treated patients have mean adult heights ranging from -2.8 to -1.7 SDS (11). Moreover, the medical therapy has been linked to substantial adverse consequences such as nephrocalcinosis, hypercalciuria, hypercalcemia, and secondary and tertiary hyperparathyroidism (12). Improper adherence to treatment with frequent phosphate dose and secondary hyperparathyroidism are two important factors that lead to inadequate metabolic control and stunted growth in children with XLHR (9). In fact, progressive disproportional stunting was revealed by a new study on the linear growth of a large cohort of XLHR patients receiving consistent calcitriol and phosphate medication (13), while the degree or the extent of leg bowing seemed to be just a weak link. This was primarily caused by consistently reduced leg growth over the prepubertal growth stage and was significantly correlated with the degree of hypophosphatemia. Trunk growth, however, was less negatively impacted in XLHR. Together, these discordant growth patterns produce a considerably raised sitting height index, and as a general rule, the shortest patients appear with the highest degree of bodily disproportion (13).

Growth Hormone treatment in children and adolescents with XLHR: Recently, regardless of a well-controlled disease, treatment with rhGH was suggested as a means of supporting growth in children with XLHR exhibiting poor growth. It is well established that growth hormone (GH) affects growth by acting through insulin-like growth factor-1 (IGF-1), which is crucial for the maturation and differentiation of growth plate chondrocytes (2), promotes the mineralization of the bone matrix, collagen secretion, and osteoblastogenesis (14). Furthermore, it is hypothesized that GH may increase serum phosphate levels by increasing renal phosphate reabsorption, both directly and indirectly via IGF-1 (15). In fact, the proximal renal tubule had been proved to have GH and IGF-I receptors. Consistent with this, research suggests that improved renal phosphorus reabsorption in association with enhanced 1α-hydroxylase enzyme activity are likely responsible for the favorable effects of rhGH treatment on phosphate metabolism (9). It is important to note that during rhGH treatment, patients with XLHR may experience an unexpected rise in the serum phosphate level due to a temporary decline in urine phosphate excretion (16). Numerous studies have demonstrated that rhGH treatment can accelerate growth in patients with short XLHR patients, particularly when initiated in the prepubertal period (5, 9, 15, 16). However, the limited patient numbers, lack of controls, absence of randomization, and very short observation periods make it difficult to judge these types of studies. Furthermore, GH may also exacerbate pre-existing body disproportion in XLHR patients, according to certain theories, as during rhGH treatment, the standardized sitting height increased by 1.6 SD compared with baseline values (17). In a retrospective longitudinal analysis study done by André et al (2) in 2022, there were two groups of children with XLHR: One that received rhGH treatment and the other that did not; the mean duration of GH therapy was 4.4 ± 2.9 years. This study is the first to clarify and corroborate the idea that GH promotes height in short kids with XLHR. It also shows that GH raises final adult height in children who continue to exhibit short stature even after receiving the best possible medical treatment. The greatest increase in height was seen throughout the first two years of treatment, and despite rhGH discontinuation, the height increase persisted until the final height was reached. Most notably, rhGH treatment enabled these children to attain a satisfactory final adult height (155.5 ± 6.3 cm in girls and 165.5 ± 6.4 cm in boys). A study conducted by Baroncelli et al. (18) in 2001, on a small number of children and teens with XLHR who received rhGH also suggests that GH treatment shows a favorable impact on final adult height. Zivicnjak et al. conducted a study in 2011 on 16 pre-pubertal children with XLHR who were short (height: −3.3 SDS), eight of whom received rhGH treatment for three years. The results revealed a considerable improvement in linear growth (+1.1 SDS) without a discernible alteration in the body proportions (13). An insightful study done by Rothenbuhler et al (5) in 2017, on 19 patients with XLHR, after two years of treatment with rhGH revealed that height SDS improved with rhGH therapy from −2.35 ± 0.8 SDS at the starting point to −1.62 ± 0.8 SDS (p=0.01) after a year and −1.2 ± 1.0 SDS (p=0.04) after two years. A substantial correlation was observed between the age at which

rhGH was initiated and the number of centimeters acquired throughout the duration of the study. Pre-pubertal children responded more favorably to rhGH. Burosumab, a human monoclonal IgG antibody that blocks FGF23's effects, has been a treatment option for XLHR since 2018 (19). Research on children demonstrated that this medication increases serum phosphate level and plasma calcitriol while restoring renal reabsorption of phosphate. In children with XLHR, it significantly improved bone malformations and rickets. But still, it seems that FGF23 blockage has little influence on growth velocity (19, 20).

In a recent appealing study, Ertl et al. (21) in 2022 conducted the first research on the growth of XLHR patients receiving concurrent burosumab and rhGH therapies. The study included 36 XLHR patients who were treated with Burosumab for a minimum of one year following conversion from traditional medical treatment. Twenty-three of them were given Burosumab exclusively, and the remaining patients maintained rhGH therapy after switching to Burosumab. After a year, children treated with Burosumab alone had only slight changes in their height SDS. In contrast, throughout the year of combination of Burosumab and GH therapy, children's height was definitely improved. This study suggests that continuing treatment with rhGH after switching from conventional therapy to Burosumab might be beneficial for the final height (21).

On the other hand, Smith and Remmington in 2021 included two studies (20 participants) in their review. The results showed that rhGH treatment could improve the height-standard deviation (SDS) score (z-score), but they were uncertain whether growth hormone or other treatments caused the transient increase in serum phosphate and maximal tubular phosphate reabsorption. They also concluded that they do not have strong enough evidence to recommend rhGH therapy for children. X-linked hypophosphatemia (22).

Conclusion:

The addition of rhGH to optimal medical treatment might represent a promising option in the significant portion of affected patients with XLHR and growth failure. Follow-up is needed until the final height is reached to evaluate the long-term benefit of rhGH treatment on final height. Further studies will be necessary to determine the most efficient treatment protocol concerning doses, duration and age of initiation or rhGH in short children with XLHR. However, further studies would be needed to study the addition of rhGH to optimal medical treatment in short children with XLHR.

Conflicts of interest: There are no conflicts of interest.

Funding: N/A

Authors' contributions:

Study conception & design: (Munib A. Al-Zubaidi and Wasnaa H.Abdullah). Literature search: (Wasnaa H.Abdullah). Data acquisition: (Munib A. Al-Zubaidi and Wasnaa H.Abdullah). Data analysis & interpretation: (Munib A. Al-Zubaidi and Wasnaa H.Abdullah). Manuscript preparation: (Wasnaa H.Abdullah). Manuscript editing & review: (Munib A. Al-Zubaidi and Wasnaa H.Abdullah).

References:

1. Laurent MR, Harvengt P, Mortier GR, Böckenhauer D. X-linked hypophosphatemia. GeneReviews®. 2023. URL

2. André J, Zhukouskaya VV, Lambert AS, Salles JP, Mignot B, Bardet C, et al. Growth hormone treatment improves final height in children with X-linked hypophosphatemia. Orphanet Journal of Rare Diseases. 2022;17(1):1-8. https://doi.org/10.1186/s13023-022-02590-5 PMid:36544157 PMCid:PMC9768884

3. Haffner D, Emma F, Eastwood DM, Duplan MB, Bacchetta J, Schnabel D, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nature Reviews Nephrology. 2019; 15(7):435-55. https://doi.org/10.1038/s41581-019-0152-5 PMid:31068690 PMCid:PMC7136170

4. Cannalire G, Pilloni S, Esposito S, Biasucci G, Di Franco A, Street ME. Alkaline phosphatase in clinical practice in childhood: Focus on rickets. Frontiers in Endocrinology. 2023; 14:1111445. https://doi.org/10.3389/fendo.2023.1111445 PMid: 36817604 PMCid:PMC9931734

5. Rothenbuhler A, Esterle L, Gueorguieva I, Salles JP, 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 Hormone & IGF Research. 2017;36:11-5. https://doi.org/10.1016/j.ghir.2017.08.001 PMid: 28822957

6. Chande S, Bergwitz C. Role of phosphate sensing in bone and mineral metabolism. Nature Reviews Endocrinology. 2018; 14(11):637-55. https://doi.org/10.1038/s41574-018-0076-3 PMid:30218014 PMCid:PMC8607960

7. Cagnoli M. Spontaneous growth and effect of early therapy with calcitriol and phosphate in X-linked hypophosphatemic rickets. Pediatr Endocrinol Rev. 2017; 17:119-22. https://doi.org/10.17458/per.vol15.2017.crb.spontaneousgrowtheffect

8. 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 Journal of Rare Diseases. 2019;14:1-25. https://doi.org/10.1186/s13023-019-1014-8 PMid: 30808384 PMCid:PMC6390548

9. Baroncelli GI, Mora S. X-Linked hypophosphatemic rickets: Multisystemic disorder in children requiring multidisciplinary management. Frontiers in Endocrinology. 2021;12: 688309

https://doi.org/10.3389/fendo.2021.688309 PMid: 34421819 PMCid:PMC8378329
10. Trombetti A, Al-Daghri N, Brandi ML, Cannata-Andía JB, Cavalier E, Chandran M, et al. Interdisciplinary management of FGF23-related phosphate wasting syndromes: a consensus statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia. Nature Reviews Endocrinology. 2022; 18 (6):366-84. https://doi.org/10.1038/s41574-022-00662-x PMid:35484227
11. Rothenbuhler A, Schnabel D, Högler W, Linglart A. Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH). Metabolism. 2020;103:153892. https://doi.org/10.1016/j.metabol.2019.03.009 PMid: 30928313
12. Laurent MR, De Schepper J, Godefroid N, Levtchenko E, Vande Walle J. Consensus recommendations for the diagnosis and management of X-linked hypophosphatemia in Belgium. Frontiers in endocrinology. 2021 Mar 19;12:641543. https://doi.org/10.3389/fendo.2021.641543 PMid: 33815294 PMCid: PMC8018577
13. Živičnjak M, Schnabel D, Billing H, Staude H, Filler G, Querfeld U, et al. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. Pediatric Nephrology. 2011; 26:223-31. https://doi.org/10.1007/s00467-010-1705-9 PMid: 21120538
14. Yakar S. Insulin-like growth factors: Actions 1 on the skeleton. J Mol Endocrinol 2018; 17-0298. https://doi.org/10.1530/JME-17-0298
15. 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;96(12):E2097-105. https://doi.org/10.1210/jc.2011-0399 PMid:21994957
16. Seikaly MG, Brown R, Baum M. The effect of recombinant human growth hormone in children with X-linked hypophosphatemia. Pediatrics. 1997; 100(5):879-84. https://doi.org/10.1542/peds.100.5.879 PMid:9346990
17. 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;113(6):e593-6. https://doi.org/10.1542/peds.113.6.e593 PMid:15173542
18. Baroncelli GI, Bertelloni S, Ceccarelli C, Saggese G. Effect of growth hormone treatment on final height, phosphate metabolism, and bone mineral density in children with X-linked hypophosphatemic rickets. J Pediatr.2001;138(2):236-43. https://doi.org/10.1067/mpd.2001.108955 PMid: 11174622
19. 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; 378: 1987-98. https://doi.org/10.1056/NEJMoa1714641 PMid: 29791829
20. 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. The Lancet. 2019;393(10189):2416-27. https://doi.org/10.1016/S0140-6736(19)30654-3 PMid:31104833
21. Ertl DA, Le Lorier J, Gleiss A, Trabado S, Bensignor C, Audrain C, et al. Growth pattern in children with X-linked hypophosphatemia treated with burosumab and growth hormone. Orphanet Journal of Rare Diseases. 2022;17(1):1-2. https://doi.org/10.1186/s13023-022-02562-9 PMid: 36371259 PMCid: PMC9652849
22. Smith S, Remmington T. Recombinant growth hormone therapy for X-linked hypophosphatemia in children. Cochrane Database Syst Rev. 2021; 10(10).https://doi.org/10.1002/14651858.CD004447.pub3 PMid: 34618915 PMCid:PMC8496964

How to Cite this Article:
Al-Zubaidi MA, Abdullah WH. Review Article: Growth Hormone Treatment's Impact on Height in Children with X-Linked Hypophosphatemic Rickets. J Fac Med Baghdad. 2024;66(3). https://doi.org/10.32007/jfacmedbaghdad.6632349Available from: https://iqjmc.uobaghdad.edu.iq/index.php/19JFacMedBaghdad36/article/view/2349

تأثير علاج هرمون النمو على الطول لدى الأطفال المصابين بالكساح الناقص الفوسفات المرتبط بالكروموسوم X

منيب احمد الزبيدي[1] , وسناء هادي عبد الله[2]
فرع طب الأطفال, كلية الطب, جامعة بغداد, بغداد, العراق
فرع طب الأطفال, كلية الطب, الجامعة المستنصرية. بغداد, العراق

الخلاصة
يعتبر الكساح الناقص الفوسفات المرتبط بالكروموسوم X هو الشكل الأكثر شيوعًا للكساح الوراثي في الأطفال، غالبًا ما يكون النمو المتقزم وقصر القامة غير المتناسب من العلامات المبكرة لـهذا النوع من الكساح. قد يستمر تأخر النمو حتى بعد تلقي العلاج التقليدي المناسب (مكملات الفوسفات ونظائر فيتامين د النشطة) حتى لو تم البدء في العلاج في وقت مبكر من الطفولة. أظهرت غالبية الدراسات أن حوالي 50٪ من الأطفال الذين عولجوا من هذا الكساح يظلون قصار القامة عند انتهاء النمو، مما يؤدي إلى طول نهائي ضعيف عند اكمال البلوغ. في الآونة الأخيرة وبغض النظر عن المرض الذي يتم التحكم فيه جيدًا، تم اقتراح العلاج بهرمون النمو البشري المؤتلف كطريقة فعالة لدعم النمو لدى الأطفال الذين يعانون من هذا النوع من الكساح والذين يعانون من نقص النمو. يُفترض أن هرمون النمو قد يزيد من مستويات الفوسفات في المصل عن طريق زيادة إعادة امتصاص الفوسفات الكلوي، سواء بشكل مباشر أو غير مباشر عبر عامل نمو الأنسولين 1. في الواقع، ثبت أن الأنبوب الكلوي القريب يحتوي على مستقبلات هرمون النمو وعامل نمو الانسولين 1.كما أثبتت العديد من الدراسات أن علاج هرمون النمو الطبيعي يمكن أن يسرع النمو لدى المرضى الذين يعانون من قصر القامة ، وخاصة عند البدء في العلاج في فترة ما قبل البلوغ. قد يمثل إضافة هرمون النمو الطبيعي إلى العلاج الطبي الأمثل خيارًا واعدًا في نسبة كبيرة من المرضى المصابين بقصر القامة في مرض الكساح الناقص الفوسفات وفشل النمو. هناك حاجة إلى المتابعة لتقييم الفائدة طويلة المدى لعلاج هرمون النمو الطبيعي على الطول النهائي. ستكون هناك حاجة إلى مزيد من الدراسات لتحديد بروتوكول العلاج الأكثر كفاءة فيما يتعلق بالجرعات ومدة وعمر بدء العلاج أو هرمون النمو الطبيعي في الأطفال قصار القامة الذين يعانون من الكساح الناقص الفوسفات المرتبط بالكروموسوم X.

الكلمات المفتاحية: الكساح الناقص الفوسفات المرتبط بالX، قصر القامة، هرمون النمو.