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Articular Manifestations of X-Linked Hypophosphatemic Rickets in Saudi Children: A Retrospective Cohort Study

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Abstract **Original Research Article**

Introduction: This retrospective cohort study aimed to describe the articular manifestations in Saudi children with X-linked hypophosphatemic rickets (XLHR). ***Materials and Methods:*** The medical records of children with XLHR were retrospectively reviewed. The diagnosis of XLHR was confirmed biochemically by low serum phosphorus and elevated alkaline phosphatase, radiologically by the evidence of active rickets and genetically by phosphate-regulating gene with homology to endopeptidases (PHEX) gene mutations. ***Results:*** Twenty-two patients with XLHR (10.8 years ± 4.9) were enrolled. All children were followed at King Faisal Specialist Hospital & Research Center for a mean duration of 8.7 years (±3.7). Clinically, all patients had disproportionate short stature (-2.5 standard deviation ±1.3) with varying degrees of skeletal deformities, including genu varum in 68%, genu valgum in 18%, coxa vara in 14%, bowing of tabia in 32%, and history of fractures in 32% of children. Hearing impairment was noted in two children. Biochemically, all patients showed increased urinary phosphate loss with hypophosphatemia 0.67 mmol/l (±0.15) and elevated serum alkaline phosphatase levels 522 IU/l (±133). Genetically, hemizygous PHEX mutation (C746F) was reported in seven patients. Radiologically, four children had osteoarthritis and three had enthesopathies. Four patients craniosynostosis. All children were on oral inorganic phosphate salts (50–70 mg/kg/day), combined with 1,25(OH)2D3 (alfacalcidol or calcitriol, 30–40 ng/kg/day). ***Conclusion:*** Patients with XLHR frequently present with varying degrees of joint deformities that are not completely resolved with either medical or surgical treatment. Long-term skeletal complications of XLHR that present in adults are less common in children and adolescents.

Keywords: Genu varum, genu valgum, bowing of legs, osteomalacia, fractures, osteoarthritis, enthesopathies hypophosphatemia, rickets.

INTRODUCTION

Inherited disorders of renal phosphate wasting denote a group of rare metabolic bone conditions with substantial musculoskeletal sequelae. X-linked hypophosphatemic rickets (XLHR) is the most common form of inherited increased renal phosphate excretion, caused by a mutation in the phosphate-regulating gene with homology to endopeptidases (PHEX), which results in early onset of severe poor bone mineralization manifested as rachitic changes at the growth plate and osteomalacia in the long bones, associated with musculoskeletal pain, lower limb deformities, disproportionate short stature, and poor dentition [1-3]. Other manifestations such as hyperparathyroidism, osteomalacia, enthesopathies, osteoarthritis, and pseudo-fractures become apparent in adulthood [2]. Furthermore, due to articular cartilage degeneration and calcification of entheses, patients develop enthesophytes and osteophytes [4]. Owing to the multisystemic nature of this metabolic bone disease, patients require regular follow-up by a multidisciplinary team, organized by a metabolic bone disease expert, including the orthopedic and rheumatology service.

XLHR presentation has been described in different ethnic groups. However, the frequency of this disorder remains very rare. We had the privilege at

King Faisal Specialist Hospital & Research Center (KFSH-RC), Riyadh to follow a large cohort of children with XLHR. In this article, we describe the articular manifestations of XLHR and highlight the importance of early diagnosis and intervention to avoid progressive joint deformities and gait disturbance.

MATERIALS AND METHODS

This retrospective cohort study comprised of all children with XLHR who were followed at KFSH-RC, Riyadh from January 2014-December 2020 Medical records of all included patients were reviewed for gender, age of first disease manifestations, and clinical, and radiological and molecular genetic findings. Patients are usually seen every 3 months with a thorough clinical assessment, including height measurement and bone deformity assessment. In addition to renal and hepatic profile, measurement of phosphate, alkaline phosphatase, intact parathyroid hormone, vitamin D levels, and tubular reabsorption of phosphate normalized to the glomerular filtration rate were also performed. All patients underwent sequence analysis of the PHEX gene. Imaging studies reviewed bone deformity, osteoarthritis, and enthesopathies [5, 6].

All collected data were anonymized and analyzed under confidentiality practice. The study has been approved by the Research Affairs Council at KFSH-RC, Riyadh.

RESULTS

Twenty-two patients were included in this study: 12 females and 10 males, mean age of 10.8 ± 4.9 (range 2–19) years and mean follow-up duration of 8.7 ± 3.7 years. The diagnosis of XLHR was made based on the evidence of active rickets with low serum phosphorus and elevated alkaline phosphatase levels and confirmed by positive PHEX mutation. The consanguinity rate was 55% of the enrolled families. Three families had more than two affected children.

All included patients had significant growth failure, with disproportionate short stature mainly affecting the lower segment because of lower limb deformities in the form of bowing of legs and tibia and knocked knees. Seven (32%) patients experienced recurrent fractures. Eight patients had poor dentition. Fourteen children completed formal audiology testing; 12 children reported normal hearing and two children showed hearing impairment.

At the time of our assessment, articular and skeletal findings revealed genu varum, genu valgum, and bowing legs; additionally, other skeletal deformities manifested by imaging studies. Table 1 shows the frequency of clinical and radiological skeletal deformities. All children had varying degrees of cupping, fraying, and irregularity of metaphyses; however, none of them had spinal stenosis.

Table 2 shows the biochemical findings. All children had serum hypophosphatemia, mild hypocalcemia, and elevated serum alkaline phosphatase levels. Decreased renal tubular ability for phosphate reabsorption was documented in all patients. Secondary hyperparathyroidism and renal calcification as secondary complications were noted in 80% and 50% of the patients, respectively.

All patients had a genetically-confirmed diagnosis: one patient was heterozygous for a duplication including Exon 3, one patient was heterozygous for a duplication including Exon 17, one patient was heterozygous for del Exon 19, Exon 20 at least 1.2 kb, three patients were heterozygous for c.846:1bp deletion of T:codon 282, three patients were hemizygous for c.1241delT, two patients were hemizygous for c.1318 G>T, two patients were heterozygous for c.214810 C>A, and four patients were hemizygous for c.2237 G>T mutation (C746F).

All patients were receiving oral inorganic phosphate salts (50–70 mg/kg/day) combined with 1,25(OH)2D3 (alfacalcidol or calcitriol, 30–40 ng/kg/day). Treatment adherence was acceptable in all the treated patients according to their medical history. Nineteen patients underwent lower limbs corrective surgeries.

Table 1: Frequency of articular and skeletal manifestations in 22 patients with XLHR

Manifestations	Frequency (%)
Genu varum	15 (68%)
Bowing of tibia	7 (32%)
Genu valgum	4 (18%)
Craniosynostosis	4 (18%)
Coxa vara	3 (14%)
Osteoarthritis	4 (18%)
Enthesopathies	3 (14%)

XLHR, X-linked hypophosphatemic rickets

Table 2: The biochemical findings in 22 patients with XLHR

Test	Results	Normal value
Phosphorous, mean (+SD)	0.67 (+0.15)	0.9–1.5 mmol/l
Calcium, mean (+SD)	2.1 (+0.16)	2.1–2.6 mmol/l
Parathyroid hormone, mean (+SD)	96 (+33)	15–60 pg/ml
25OH vitamin D, mean (+SD)	35 (+14)	>50 nmol/l
Alkaline phosphatase, mean (+SD)	522 (+133)	60–300 U/l
TmP/GFR	0.66 (+0.1)	1.15–2.44 mmol/l

SD, standard deviation; TmP/GFR, tubular reabsorption of phosphate normalized to the glomerular filtration rate; XLHR, X-linked hypophosphatemic rickets

CONCLUSION

Our cohort showed the outcome of a group of children with genetically proved XLHR and relatively long-term follow-up. However, they had variability in the frequency of articular and skeletal manifestations, which are in line with the previous reports [11]. Currently, there is no cure for such disorders. Our patients were adequately treated with conventional therapy: phosphate salt and vitamin D analogues. Despite of this, most of them required several corrective surgeries. Unfortunately, they continued to have gait impairment and joint deformities. The majority of them had bowing of the legs, affecting their height and associated with pain during walking. The severity of musculoskeletal symptoms was also variable [12]. Adult patients with XLHR can be affected by skeletal complications related to spontaneous fractures due to persistent osteomalacia and early osteoarthritis and enthesopathies. In our group of adolescents, four patients had such complications [12]. This might suggest that long-term skeletal complications are less common in children and adolescents. Studies suggest that severe deformities of the lower limbs can be improved by surgery at all ages. Recurrence of deformities in the lower limb might happen and it is independent of the correction procedure used. Furthermore, the deformity progression tends to decline after physical maturity is attained [3].

This report highlights the importance of multidisciplinary team evaluation of these children for early assessment and management of these joint deformities.

Our study's main strengths include the large data with long-term follow-up. However, this study has limitations and results should be interpreted carefully. The study is a retrospective analysis of collected data from patients diagnosed over a long period. Furthermore, patients' selection bias cannot be ignored.

Author Contributions

All the authors were equally involved in the curation and development of this manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest: No conflict of interest

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