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X-Linked Hypophosphatemia at the European Society of Pediatric Endocrinology Meeting 2022

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Abstract

Rickets, a growth plate disorder, is classified into calcipenic and phosphopenic types based on the etiology. Phosphopenic rickets can be further classified into fibroblast growth factor 23 (FGF23) mediated and non-FGF23 mediated. FGF-23 has a phosphaturic effect which results in hypophosphatemia and, therefore, the accumulation of hypertrophied chondrocytes, leading to rachitic changes in the bones. One of the most common causes of inherited hypophosphatemic rickets is X-linked hypophosphatemia (XLH), mainly due to a mutation in the *PHEX* gene that ends in the extended release of FGF-23. During the 60th annual meeting of the European Society for Pediatric Endocrinology, held in Rome between September 15 and 19, 2022, approximately 15 presentations were made either as free communication or poster. In addition, there was a dedicated satellite symposium focusing on XLH. This article has been prepared mainly to share knowledge and updates discussed during the meeting about hypophosphatemic rickets, as we feel this disease is still to be focused on in the MENA region, since there are some gaps in the recognition and management of FGF23 hypophosphatemic rickets and osteomalacia.

Keywords
- bone deformities
- bone disorders
- fracture
- congenital and genetic diseases
- rickets
- short stature
- X-linked hypophosphatemia

Introduction

During the 60th annual meeting of the European Society for Pediatric Endocrinology (ESPE), held in Rome with a theme of "Personalized Medicine in Paediatric Endocrinology," several important pediatric endocrine topics were discussed, including bone growth disorders. The bone and growth plate working group had arranged excellent talks delivered by eminent speakers.[1] We are focusing in this paper on hypophosphatemic rickets, for which we have summarized the main aspects that were mentioned or discussed. Clinicians and researchers from different countries also presented several e-posters. Therefore, the conference highlights will shed the light on the following main aspects: (1) etiology and

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genes, (2) treatment and impact, and (3) ongoing management, aiming to contribute to reducing the already recognized gaps in the treatment modalities/treatment pathway, treatment outcomes, mortality, and health care resource utilization in the Middle East,[2] especially with the increased number of diagnosed cases from the region[3] and the desire to raise the awareness on the recognition and modern management of X-linked hypophosphatemia (XLH).[4]

Conference Highlights

Etiology and Genes

Maria Thomas highlighted the need to consider the appropriate phosphate level based on age and gender, revising local laboratory references when diagnosing hypophosphatemia. She raised this concern through a case of a 4-year-old girl who was misdiagnosed with Blount's disease (disorder of growth plate) and later found to have XLH rickets. Her phosphate level was low throughout, but it was undetected as it fell within the normal reference range of the U.K. Pathology Harmony Group (PHG). PHG initiated a project in the United Kingdom in 2007 to harmonize the reference ranges across the U.K. laboratories. However, by comparing those reference intervals with the Canadian laboratory initiative on pediatric reference intervals, it was highlighted that a good number of hypophosphatemic patients could have gone unrecognized when the laboratories were using inappropriate lower cutoff values. Sejin Kim et al had presented a poster revealing a novel variant of PHEX (c.667dup [p.Asp223GlyfsTer15]) in a Korean 39-year-old mother and her 12 months old infant. The mother had the typical clinical, biochemical, and radiological findings of XLH. Although the daughter was asymptomatic, she had abnormal biochemical and early radiological findings, which allowed early treatment with conventional therapy. Mehmet Eltan et al from Marmara University in Turkey shared the etiological analysis of hypophosphatemia in their center. The study included 34 patients from 26 families who underwent single-gene sequencing, if it was negative then they would proceed with multiplex ligation-dependent probe amplification (MLPA), and next-generation sequencing (NGS) techniques. Combining these three techniques resulted in identifying 87% of the molecular pathology in the cohort. MLPA itself had an additive value of 5%. The molecular etiology of the patients showed PHEX (46%), SLC34A3 (17%), FAM20C (5%), CLCN5 (5%), SLC2A2 (5%), and DMP1 (5%). Thirteen percent of the cohort did not test positive for any genetic mutation. Although PHEX gene defects were the most frequent genetic cause for hypophosphatemia, NGS demonstrated rarer molecular etiologies in the majority of the remaining patients.

Elisa Sala et al from Milan, Italy, suggested that pain might be the only presenting symptom of XLH. She reported a case of a 13-year-old boy with normal height, weight, and none of the XLH bone deformities who presented with bilateral knee pain for 2 years. The challenge in his diagnosis was normal joint X-rays despite a background of the suspicious biochemical profile including hypophosphatemia, hyperphosphatasia, hyperphosphaturia with reduced tubular reabsorption of phosphate, and hypercalciuria. Magnetic resonance imaging knee was performed, and it showed features of rickets in the distal femoral epiphysis, for which the treating physician proceeded with genetic testing that confirmed *SLC34A3* gene mutation that is responsible for hereditary hypophosphatemic rickets with hypercalciuria. Revealing this genetic diagnosis was extremely important as such patients should not be given an active form of vitamin D to avoid complications such as hypercalcemia, nephrocalcinosis, and renal damage. Holly Hester et al from Leeds—United Kingdom presented a poster of a 12-month-old girl with rickets who had a delayed genetic diagnosis. Her biochemical investigations showed initially hypophosphatemia, high alkaline phosphatase, mild hyperparathyroidism, elevated 1,25 vitamin D with markedly elevated FGF23 with incalculable urinary calcium:creatinine ratio, as the urinary calcium was 1.8 but undetectable urinary creatinine. Repeating the tests after giving the conventional therapy showed normalization of FGF23 and the intact FGF23 was even low. Proceeding with genetic testing revealed a novel mutation of *SLC34A3* gene. The learning message from this case was to focus on the measurement of intact FGF23 in such cases as the C-terminal FGF23 do have a longer half-life compared with the biologically active molecule "intact FGF23." Genetic testing has helped in stopping the alfacalicdol which could result in renal damage. Hypercalciuria should not be overlooked by having undetectable urine creatinine.

The role of iron deficiency in hypophosphatemic rickets was thoroughly explained by Prof Erik Imel. Normally, there is a cleavage site on FGF23 to allow degrading it even before its release from the osteocytes. This mechanism occurs regularly and frequently. In patients with autosomal dominant hypophosphatemic rickets where the mutation in FGF23 resulted in an issue with the cleavage, therefore active FGF23 all the time, increasing gene expression because of iron deficiency will result in more functionality of FGF23, resulting in more phosphaturia and hypophosphatemia. Treating those patients with oral iron supplements will reduce the *FGF23* gene expression, and it will result in a better phosphate level. Interestingly, it was explained that using certain intravenous formulae may worsen the condition as with ferric carboxymaltose that would stop the cleavage of FGF23 and prevent its degradation, whereas no issue with iron dextran formula. *FGF23* gene expression was also stimulated by hypoxia and erythropoietin.

Treatment and Impact

In France, the final heights (FHs) of 398 patients with XLH over the last decades were studied by Dr Anya Rothenbuher and her team. The study included patients born between 1950 and 2006. Mean height SDS improved over the generations, the mean male height was 156.3 cm which had improved to 165.1 cm for adults born after 2000. Similarly, the mean female final adult height improved from 148.6 to 154.7 cm. FHs for both male and female XLH patients had markedly increased over the last decades in France, possibly reflecting better overall disease management and including

developing specialized reference centers for rare diseases running multidisciplinary clinics.

Prof. Annemieke Boot presented another analysis of the International XLH Registry (12 countries), describing baseline characteristics of children treated with conventional therapy and burosumab. She noted the difference in treatment across European countries. In total, 58.7% of the recruited patients were using burosumab. It was noted that the mean time from first symptoms to XLH diagnosis was 1 year, which was similar in both burosumab and conventional treatment groups. Patients in the burosumab group reported more craniosynostosis, genu valgum, nephrocalcinosis, and excessive caries at baseline than children treated with conventional therapy, indicating those patients with more severe course had the chance to be started on burosumab than others.

From the data of 15 Italian patients live with XLH, Dr Giampiero Baroncelli presented a poster about the impact of burosumab on the phosphate metabolism and bone health of XLH patients. Major improvements were noted biochemically and radiologically.

On-going Management

Dr Mirko Rehberg reported moderate improvements in muscle function after the initiation of burosumab treatment. The study included 11 patients (age: 9.6 ± 3.4 years) monitored over a number of intervals, with an endpoint of 24 months of burosumab treatment. No improvement in clinical and functional parameters during conventional therapy was observed. However, by receiving burosumab treatment, there was an improvement in grip strength, chair-rising, and 2-leg jump tests. Despite burosumab being a bone therapy, it had shown improvement in muscle function by (1) improving bone health and growth which ultimately improves strength and dynamics, and (2) phosphate homeostasis plays a role in ATP generation which again reflect on muscle strength.

Dr. Adalbert Raimann from Austria studied the quality of life (QoL) of patients with XLH and suggested that the disease burden often is underestimated. Elevated body mass index and the number of osteotomies were associated with poorer QoL (inverse relation). Saying that QoL improved in patients on burosumab treatment for more than 1 year.

Data analysis from the German XLH registry for patients between 1 and 18 years with a confirmed genetic diagnosis (93 patients) presented by Dr Rohberg concluded that burosumab treatment was equally effective in healing active rickets based on ALP z-scores in adolescents as in children with XLH. Adolescents in this cohort were given lower weight-based burosumab doses than children, phosphate level normalized in only 40% of the cohort after 12 months of treatment, associated with elevated PTH levels. This study suggested that complete normalization of serum Pi levels is optional to achieve rickets resolution, and the main focus should be on ALP. Number of comments raised by the audience questioning to increase the burosumab dose in the adolescent population to improvise the phosphate and normalize the parathyroid hormone level.

Patient-reported outcomes from a randomized open-label phase 3 trial comparing burosumab versus conventional therapy in children with XLH (24-week extended period from week 64) were presented by Dr. Raja Padidela. At this stage, all patients were on burosumab, and 26 patients continued to week 88. Pain interface and fatigue were less among patients on burosumab and improved on week 88 for the crossed-over group whom being on conventional therapy up to week 64. Similarly, physical and psychosocial health got better.

Conclusion

Genetic testing can be extremely helpful in reaching the correct diagnosis and therefore prevent unwanted complications in some cases of hypophosphatemic rickets. Having a registry for this condition helps in understanding the natural history of the disease, patients' QoL and their needs. Diagnosed people with XLH these days are having a better adult height compared with diagnosed people from last decades reflecting on better overall disease management, including developing specialized reference centers for rare diseases running multidisciplinary clinics. Burosumab was found to have an important role in improving muscle function, pain, fatigue, and QoL. The conference was very educative and provided a good opportunity for meeting experts, networking, and collaboration.

Authors' Contribution
All the authors contributed equally to the perception, drafting, and finalizing of the report.

Compliance with Ethical Principles
Not applicable.

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Conflict of Interest
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