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On X-Linked Hypophosphatemia at the European Society of Pediatric Endocrinology Meeting, Vienna, Austria; September 19–21, 2019

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Abstract

X-linked hypophosphatemia (XLH) is the most common form of inherited hypophosphatemic rickets. Phosphate wasting results in weak, soft and deformed bones, impaired growth, and affected mobility. It is mainly caused by a loss of function mutation in PHEX gene that leads to elevated fibroblast growth factor-23 which mediates the phosphate wasting. During the 58th annual meeting of the European Society of Pediatric Endocrinology (ESPE) held in Vienna between September 19, 2019 and 21, 2019, nearly 100 free communications and a dedicated symposium focused on XLH. The authors attended the conference and wished to share its highlights pertaining to XLH and burosumab therapy to extend the benefit to other professionals who did not attend.

Keywords: Bone deformities, bone disorders, fracture, congenital and genetic diseases, rickets, short stature, x-linked hypophosphatemia

Introduction

Rickets can be classified into calcipenic and phosphopenic types. The phosphopenic type is further subdivided into phosphaturic and nonphosphaturic subtypes.[1-3] The phosphaturic subtype can be either fibroblast growth factor-23 (FGF-23) mediated or non-FGF23 mediated. One of the main causes of FGF23-mediated hyperphosphaturic hypophosphatemic rickets is the X-linked hypophosphatemia (XLH). XLH is an X-linked dominant inherited disorder due to the mutation in PHEX gene on the X chromosome. Characteristically, X-linked inheritance cannot be passed by fathers to their

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sons. It usually manifests in the first 2 years of life.[1-3] Patients with XLH could have bone pain, skeletal deformities secondary to rickets, short stature, dental abscesses and hypodense dentin, muscular insufficiency, craniosynostosis, and hearing defect.[1-3]

During the recent 58th annual meeting of the European Society of Pediatric Endocrinology held in Vienna between September 19, 2019 and 21, 2019, nearly 100 free communications (oral and posters) were concerned with bone, growth plate, and mineral metabolism. Furthermore, one symposium was dedicated to "Growing up with XLH: A multidisciplinary approach." The authors attended the conference and wish to highlight selected contents pertaining to XLH and burosumab therapy to extend the benefit to other professionals who did not attend. The abstracts of the presentations are available on line.[4]

Conference Highlights

Genotype, diagnosis, and investigations of X-linked hypophosphatemia

Susanne Thiele *et al*. (Germany) highlighted the broad phenotypic spectrum of XLH. It can range from just isolated hypophosphatemia with no clinical signs up to severe disease that leads to extreme limb deformities, disproportionate short stature, and distinct tooth defects. They also underscored the importance of the delay in diagnosing XLH which leads to a remarkable impact on patients. They suggested using a new tool to diagnose XLH and also other renal phosphate wasting disorders using the next-generation sequencing (NGS). It was claimed to be reliable, cheaper, and quicker than older methods. Their tool was able to detect a PHEX mutation presenting as mosaicism. As a result, patients could be counseled properly and allowed to be started on appropriate therapy. The team reviewed the molecular genetics of 52 DNA samples sent to the University of Luebeck, for over the past 12 years. All patients were diagnosed with XLH either clinically or biochemically, and all (except 3) had molecular genetic changes in the PHEX gene revealed by Sanger sequencing in their local laboratory. Then samples were anonymously analyzed by a partner company, Bioglobe, who developed the new NGS panel which covers PHEX and ten other genes (FGF23, DMP1, ENPP1, SLC34A3, CLCN5, SLC34A1, SLC9A3R1, FAM20C, FGFR1, and KL) confirming previous genetic diagnosis and revealing more details.

Kristina Kulikova *et al*. had a poster demonstrating the clinical features as well as the genotype of XLH of 168 patients. They aged from 2 months to 56 years; females were 111 and males were 57. Their age at the diagnosis ranged between 2 months and 17 years. Out of the 137 affected families, 116 sporadic cases were identified. The clinical features showed 90% with deformities of their leg bones, 75% has muscle weakness, 72% with multiple dental abscesses, and 62.7% with short stature. PHEX mutation was the major mutation detected in 143 participants, of which 70 novel mutations were identified. Other mutations were also recognized.

Adalbert Raimann *et al*. from Austria and Germany proposed that ultrasound may be a potential alternative to quantify the onset and severity of the XLH. They reported a study on 8 patients with XLH who were compared with 13 matched controls. The distal radius and the central distal tibia were scanned by the bone ultrasound. They found that the velocity of the first arriving signal measured in bi-directional axial transmission significantly lower in XLH patients compared to the controls. They concluded that this radiation-free method could be a good option for monitoring and evaluating bone health quality and health. Indeed, more studies in this field would add benefit, especially if it determines whether the measure correlates with disease severity. Suma Uday *et al.* from 3 UK tertiary centers explored the role of serum alkaline phosphatase (ALP) in the assessment of the severity of rickets in XLH patients on conventional therapy. Forty genetically-confirmed XLH patients who had ≥3 radiographs of knees and wrists were examined. Thacher scoring and rickets severity scores (RSSs) were measured by a radiologist and a consultant in metabolic bone disease who both reviewed the radiographs. The median age of the patients

was 9.3 years (range 0.8–18.9); 48% of them were diagnosed within the first year of life. The median follow-up duration was 7.2 years. The mean knee RSS and Thacher score at baseline were 1.9 ($n = 19$) and 3.3 ($n = 8$), respectively, and at most recent follow-up visit were 1.6 ($n = 26$) and 2.4 ($n = 6$). The mean ALP z score at the diagnosis and most recent visit was 4.2 ($n = 36$) and 4.1 ($n = 34$), respectively. They concluded that the severity of rickets cannot be predicted by the rise of ALP as there was no significant correlation between ALP z-score and severity of the disease. Hence, the ALP only as a single indicator of rickets activity is limited. Studying this cohort of children with severe rickets, the authors were convinced that conventional therapy does not have a full effect on a significant improvement of the biochemical and radiological features of XLH.

Renata Pinto *et al.* from Brazil reported a 6-year-old child diagnosed with XLH confirmed to have PHEX mutation. Poor adherence over the 4 years to conventional therapy was reported due to gastrointestinal side effects of oral phosphate supplementation. The patient was scheduled to start Burosumab as soon as the drug will be available in Brazil. Their poster described the typical course of children with XLH rickets. It also highlighted that education on oral phosphate supplementation is needed to avoid gastrointestinal side effects.

Burosumab management of X-linked hypophosphatemia: trials and experiences

The results of phase 2 and 3 trials of using burosumab in the treatment of XLH were presented. Other delegates also shared their experience of treating with conventional therapy where they replace the phosphate and give active forms of Vitamin D from the various parts of the world.

W. Högler shared the results of a collaborative work (from 8 countries). They found that burosumab resulted in a greater improvement in phosphate homeostasis, rickets severity, lower limb deformity, and growth (length/height Z-score) in children with XLH. They have reported a sub-analysis from a phase 3 study (CL301(NCT02915705). Burosumab starting dose was 0.8 mg/kg rather than 0.4 mg/kg every 2 weeks. Overall, they have observed a great improvement for both younger and older children with XLH during burosumab than those who continued with conventional therapy. Furthermore, Linglart *et al*. (France, Austria, the UK, and the USA) emphasized their previous report about the effect of burosumab on the improvement of the phosphate homeostasis and rickets in children with XLH. The long-term results from phase 2 study were shared. Fifty-two prepubertal children with XLH, aged 5-12 years-old, were randomized 1:1 to receive subcutaneous burosumab, either every 2 or 4 weeks for 16 months, followed by switching all candidates to receive burosumab every 3 weeks and they continued their study for almost 3.5 years. Nearly 96% of the cohort achieved a normal serum phosphorus level (3.2–6.1 mg/dL) by week 160. RSS improved by 16 months and maintained afterward. Similarly, with regard to the improvement in the Radiographic Global Impression of Change, the improvement was observed during the mid-duration of the study and maintained afterward. The height Z-score also showed significant yet mild improvement (+0.3 standard deviation over the 3 years of therapy). Overall, the research team had concluded that long-term burosumab in children with XLH was associated with continued improvement in rickets, leg deformities, growth, and pain scores, as well as sustained improvement in mobility and normalization of phosphate homeostasis. Only 1 patient had a serious side effect that required brief hospitalization, symptoms resolved within a week and did not lead to treatment interruption. Furthermore, Annemieke Boot from the Netherlands described the progress of 11 transitioned girls from the above-mentioned Phase-2 trial. The girls had developed the fusion of their growth plates at the distal femur and proximal tibia. Their serum phosphorus levels were maintained throughout the study; they functioned better physically with less pain. Their leg deformities and growth had improved.

Volha Zhukouskaya *et al*. (France and Italy) shared their experience of switching 45 children with

XLH from conventional therapy to burosumab (0.4 mg/kg). They recommended adjusting burosumab dose according to the severity of XLH; they had to give a dose up to 2 mg/kg or 90 mg to achieve normalization of the serum phosphate levels for these patients. Importantly to say, they have not observed severe adverse events or elevated phosphate levels with that high dose. The most frequent side effects are redness at the sites of injection, abdominal, muscular, and bone pain. Jessica Sandy reported radiological, biochemical, and functional improvements over 12 months from starting Burosumab in 8 children with XLH. Interestingly, despite saying there was a general improvement, but the mean pediatric quality of life score (PEDsQL) had improved initially from 69 at baseline to 81 at 9 months; it dropped back to 67 by 12 months! (n = 7, maximum score 100).

XLH is suspected to be increased in the Arabian gulf region and two presentations were made from this region.[5] Afaf Al-Sagheir from Saudi Arabia presented a poster about a journey of a patient who was diagnosed with XLH at 4 years of age and followed up to the age of 20. The patient was treated with oral phosphate (30–50 mg/kg TDS) and Alfacalcidol (1.5–3.0 µg OD). Over this lengthy course of the treatment, the patient had developed medullary nephrocalcinosis at the age of 9 and a large parathyroid adenoma at the age of 20 which required surgical intervention. Those complications believed to be secondary to conventional therapy. Treatment was discontinued. Dr. Al-Sagheir accurately thought a new model of treatment for that FGF23 excess with less side effects is desirable. Furthermore, Fahad Al-Juraibah *et al*. presented their experience of using burosumab in 4 children after an unsatisfactory treatment with conventional therapy. Serum phosphate level showed a response after the first injection of burosumab and it normalized in 3 months for all patients. No adverse effects were observed.

Growth hormone therapy in X-linked hypophosphatemia

Julia André *et al*. (France and Italy) investigated growth hormone (GH) treatment in 34 patients (13 males/21 females). Their mean age at the start of recombinant human GH (rhGH) treatment was 9.8 years. The duration of rhGH treatment was 3.4 years. It is noteworthy that high doses of rhGH were used; mean doses of rhGH at initiation and the end of treatment were 77.4 and 66.8 µg/kg/day, respectively. They observed a height gain in the first 2 years of treatment (from −2.4 to −1.5 SDS, $P < 0.001$), which was sustained thereafter reaching a final height −1.2 SDS $P = 0.67$ despite treatment interruption. Furthermore, Aleksandra Rojek *et al.* (Poland) presented a 13-year-old girl diagnosed with XLH at the age of 7, who was found later to have GH deficiency on rhGH therapy from the age of 10 resulted in a height gain of +0.4 SDS.

Prevalence and prediction of obesity

Volha Zhukouskaya *et al.* aimed to focus on identifying the prevalence of obesity and associated factors in 172 children with XLH. A higher body mass index was observed in those with longer duration of treatment and absent family history of XLH. One-third of the cohort was either obese or overweight. Preventive measures and monitoring of patients to prevent metabolic syndrome in addition to their preexisting morbidities.

Long term evolution X-linked hypophosphatemia on conventional therapy

There are some disorders that have been reported to be associated with prolonged conventional therapy, for example, secondary hyperparathyroidism and nephrocalcinosis. Camille de Truchis (France) attempted to identify the prevalence of nephro calcinosis in a large cohort of pediatric patients diagnosed with XLH who received conventional therapy. Forty-seven of the 117 patients (40.2%) developed nephrocalcinosis after 6.6 years of the conventional treatment, whereas in adult XLH-treated patients, the prevalence is about 25%–40%. Nephrocalcinosis was associated with exposure to higher doses of phosphate supplements at the diagnosis using ultrasound kidneys (44.2 mg/kg/day). Moreover, "the dose of phosphate administered during 4 years before the study evaluation was significantly higher in patients with nephrocalcinosis than in patients without, i.e., (49.9 mg/kg/day) versus (42.2 mg/kg/day) as

per the clinical practice recommendations for the diagnosis and management of XLH. This cohort of patients had also developed some other morbidity: 23.3% had craniosynostosis, 27.9% had Chiari malformation, and 50% had dental abscesses. Those associations also reflect the severity of the disease.

Other causes of hypophosphatemic rickets

Other pathologies could lead to phosphate wasting, not necessary to be FGF23 mediated were also presented in the conference. Esin Karakilic-Ozturan *et al.* from Turkey reported two siblings with hereditary hypercalciuric hypophosphatemic rickets, a rare autosomal recessive disorder, resulted from loss-of-function mutations in the sodium-phosphate-cotransporter NPT2c. It is characterized by increased renal calcium and phosphate loss. One of the siblings had suffered from recurrent fractures in addition to bowing of legs, muscle weakness, and short stature. Sanaa Sharari described a 22-month-old patient diagnosed with Fanconi Bickel syndrome from Qatar, an autosomal recessive condition, a rare form of glycogen storage disease, caused by the mutations in the SLC2A2 gene. The SLC2A2 gene encodes for GLUT2, which plays a role in glycemic homeostasis. This described patient presented with "hepatomegaly, ricket changes, failure to thrive, developmental delay, and severe proximal tubular dysfunction. Hyperglycemia with low C-peptide levels was evident. Urine analysis showed proteinuria, glycosuria, phosphaturia, and aminoaciduria. Selmen Wannes *et al.* reported 4 cases from 2 Tunisian families with hypophosphatemic rickets. One family had 3 members with SLC34A1 gene mutation, which is characterized by hypercalciuria in addition to other biochemical markers of hypophosphatemic rickets. The other family had a 2-year-old child with FGF23 activating mutation gene. D Tessaris *et al.* reported a 3.6-year-old Italian child who presented with cardinal clinical features of rickets found to be hypophosphatemic and hyperphosphaturic. Genetic investigations revealed a heterozygous mutation in ENPP1 locus, responsible for a rare autosomal-recessive disease. Active vitamin D tablets 250 ng and inorganic phosphorous salts tablets 195.6 mg were started. Later, the patient developed the calcification of the aortic valve and bilateral conductive hearing loss, lower limb pain, fatigue, and dental enamel disturbances. These reports highlighted the importance of analyzing urine for calcium, glucose, and protein in addition to phosphate and of course the acidity for all patients with hypophosphatemic rickets as it could give the clinician a clue about the underlying pathology.

Conclusions

The advances in the management of XLH occurred at different levels. New diagnostic tools like the gene panels that help in differentiating the different disorders that lead to renal phosphate wasting became available. The new ultrasound bone techniques help in quantifying the onset and severity of XLH. Clinicians from different parts of the world shared their experience about treating XLH conventionally or by using the new treatment, burosumab. The effects of burosumab seem promising. Some morbidities can result from a long-term use of conventional therapy. Other morbidities can be associated with XLH as part of the nature of the disease, therefore it is important to be aware of all of them either to avoid when possible, or to manage them in a timely manner.

Authors' contribution

The authors provide equal contribution to the perception, drafting, and finalizing the report.

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Nil.

Conflicts of interest

Dr H Alsaffar served on as an advisory board member for Kyowa Kirin and Prof. A Linglart received honoraria for research and travel from Kyowa Kirin.

Compliance with ethical principles

Not applicable.

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