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Gulf X-Linked Hypophosphatemia Preceptorship: July 4–6, 2019, Bicêtre Paris Sud Hospital, Paris, France

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Abstract

X-linked hypophosphatemia (XLH) is an inherited disorder characterized by low levels of phosphate in the blood. Phosphate levels are low because phosphate is abnormally processed in the kidneys, which causes urinary phosphate wasting and leads to rickets in the young patients and osteomalacia in adults in addition to several other complications thereof. A 3-day conference was hosted by the Rare Diseases Unit of the Bicetre Paris Sud Hospital on July 4–6, 2019. Presentations covered the subject in a comprehensive manner spanning physiology, clinical presentations, disease burden, and the latest in the management of the XLH and its musculoskeletal, neurosurgical, obstetric, and other complications in both children and adults. Several illustrative and challenging cases were presented and discussed. The authors attended the event and would like to present a personal perspective to highlight the proceeding of the conference to extend the benefit to others who did not attend it.

Keywords: Bone deformities, bone disorders, congenital and genetic diseases, endocrine diseases, fracture, kidney and urinary diseases, rickets, short stature, X-linked hypophosphatemia, X-linked hypophosphatemic rickets

Introduction

X-linked hypophosphatemia (XLH) is an inherited disorder characterized by low levels of phosphate in the blood because of abnormal renal causing uncontrolled loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets). XLH is usually diagnosed in childhood. Features include bowed or bent legs, short stature, bone pain, and severe dental pain. XLH is caused by mutations in the PHEX gene on the X chromosome, and inheritance is X-linked dominant. Treatment generally involves supplements of phosphate and high-dose calcitriol (the active form of Vitamin D) and may also include growth hormones, corrective surgery, and dental treatment. The long-term outlook varies depending on severity and whether complications arise. While some adults with XLH may have minimal medical problems, others may experience persistent discomfort or complications.

"Assistance Publique-Hôpitaux de Paris" is the largest university hospitals' network in Europe, which includes 12 hospital groups located in the Paris region. Paris-Sud University Hospitals are composed of three hospitals: Antoine-Béclère in Hauts-de-Seine, Bicêtre, and Paul-Brousse in Val-de-Marne. The hospital group offers a complete health care, characterized by strong complementarities in terms of pediatric–adult care, within the framework of hospital–university excellence. France is the first country in the European Union which set up and implemented national plans for rare diseases including XLH.

The Rare Diseases Unit of the Bicetre Paris Sud Hospital hosted a dedicated preceptorship for 2½ days (July 4–6, 2019). The event unconditionally sponsored with Kyowa Kirin Pharma FZ-LLC. Unfortunately, it was not accredited for any continuous medical education credits. The aim was to increase awareness of the physicians of the disease burden, improve

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early recognition and optimize the clinical management of XLH in the Gulf region. The educational objectives of the preceptorship are set out in Table 1 and the highlights of the individual days are shown in Table 2. Most physicians (both adult and pediatric endocrinologists) came from several Gulf countries together with some from Eastern Europe. Speakers were mostly from the hosting center, clinical cases were presented by selected delegates, and some of the sessions were jointly moderated by Gulf and French physicians.

Conference Highlights

Session 1: Rickets, pathophysiology and diagnosis

Physiology of phosphate homeostasis

Very appropriately, Professor Justine Bacchetta started with an overview of the physiology of phosphate metabolism [Figure 1]. It was highlighted that exogenous regulators of phosphate may include; diet, season, time of the day as those can affect 1, 25 vitamin D level. In diet, it is noteworthy recognizing that 1 yogurt cup contains about 150 mg of calcium; so, during puberty when there is a rapid growth, the child may need up to 10 yogurt cups to meet the requirement. Obviously, fizzy drinks have much more of phosphate comes from the phosphoric acid, which gives soft drinks a tangy flavor and prevents the growth of mold and bacteria, which can multiply easily in a sugary solution. The normal range of serum phosphate level is variable according to the age group; so, clinicians have to pay attention to that before interpreting the results. Justine then referred to Dominique Prié's article where he wrote about phosphate homeostasis, shedding the light on mutations affecting the genes encoding the renal phosphate transporters or proteins regulating phosphate transport activity; nevertheless, the role of fibroblast growth factor (FGF)-23-Klotho axis in regulating phosphate levels and its involvement in phosphate disturbance in chronic kidney disease was described. It was important to know that hyperphosphatemia can induce cardiovascular pathology therefore reduces the longevity. Growth hormone therapy increases phosphate absorption via the insulin growth factor 1, subsequently, leading to increasing FGF-23. On the contrary, dopamine, steroids, Klotho and FGF-23 inhibit phosphate reabsorption. Infants with cow-milk protein intolerance who are treated by special milk formula eg. Neocate, are at higher risk of developing hypophosphatemia due to the very low phosphate content in such formulas[LE1] [ah2]. Patients on antacids or proton pump inhibitors could have less intestinal phosphate absorption. For further readings, please go through references.[1-5]

Hypophosphatemic rickets: Pathophysiology and clinical presentation

Professor Jean-Pierre Salles described the XLH and how it happens. Interestingly, FGF-23 levels were observed to be higher in cases of McCune Albright patients compared to XLH and that is possibly related to GNAS mutation. High phosphate intake leads to secondary hyperparathyroidism

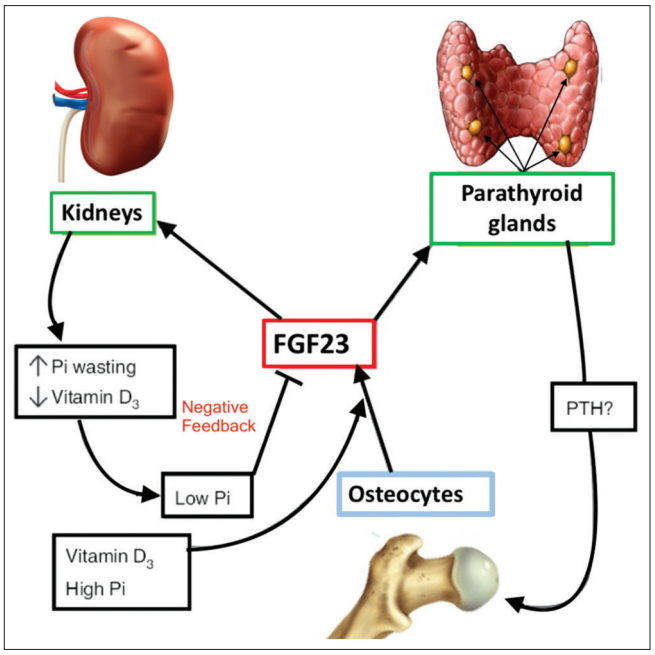

Figure 1: Illustration of phosphate homeostasis and its regulation

Table 1: The declared educational objectives* of the GULF X-linked hypophosphatemia preceptorship

To explore the aspects of hereditary rickets and nutritional rickets
To understand the XLH pathophysiology and the role of FGF23
To understand the Multidisciplinary approach in treating XLH rickets patients
To compare and contrast conventional therapy versus new horizons in XLH treatment
To discuss and review some patient cases
To overview the European/French and Gulf countries Burosumab experience

*Unfortunately, the event was not accredited with any CME hours. To the best of the authors' knowledge, the contents of the event are compliant with CME accreditation requirements of any regulatory body. XLH: X-linked hypophosphatemia, FGF 23: Fibroblast growth factor 23

to facilitate phosphate excretion in the urine. When assessing hypophosphatemia, circadian variation should be taken into consideration as low phosphate can be just pseudohypophosphatemia. Calcitriol and active Vitamin D increases FGF-23 in XLH patients. In a response to a delegate, Professor Justine Bacchetta (France) thought it would be a bad idea to reduce or counteract KLOTHO as the cardiovascular risk would increase.[6]

Genetics of rickets

Professor Outi Mäkitie (Finland) described the genetics of different types of rickets. FGF-23 can interact with various receptors; so, it binds in a KLOTHO-dependent fashion to FGF receptors (FGFRs) 1, 2, and 3 and it binds to FGFR-4 independently of KLOTHO. Therefore, we gather from that there is a close relationship between FGF-23 and KLOTHO, hence KLOTHO deficiency can give similar phenotype of FGF-23 deficiency. It is one hormone but several receptors, one co-receptor and various effects. Rickets can be classified

Table 2: Highlights of the plenary sessions on X-linked hypophosphatemia

Day 1. Basics, diagnosis, and management
Phosphate homeostasis
Hypophosphatemic rickets: pathophysiology and clinical presentation
Genetics of rickets
Clinical Cases (*Not* XLH): 1-a-hydroxylase deficiency and 25-hydroxylase deficiency
Illustrative typical clinical case of XLH
Radiological diagnosis of XLH
Clinical presentation of XLH in children
How to improve growth in XLH children
XLH from childhood to adulthood, how to succeed in transition?
Management of pregnancy and newborns
Day 2. Burden of disease and management
Endocrine features in adults
Vitamin D in XLH and other rickets
Rheumatological complications and management
Neurosurgical complications of rickets
Dental features in XLH and other rickets
ENT features in XLH and management
Conventional therapy: initiation, adjustments, and outcomes
Limit the effect of FGF23 to treat XLH? How?
Expectations of patients
Clinic cases from the Gulf region
Day 3. Clinical workshop
Clinic cases on differential diagnosis, management challenges, quiz, summary, and overview
Individuals are listed in order of presentation in the schedule

XLH: X-linked hypophosphatemia

into calcipenic and phosphopenic; calcipenic is either due to nutritional causes, or defective Vitamin D metabolism or defective Vitamin D function. Light was shed on hereditary Vitamin D dependent rickets (VDDR)-alopecia disorder, in this condition the 25 Vitamin D level can be variable from patient to other but they all characteristically have very high 1, 25 Vitamin D >350 nmol/l. Phosphopenic rickets can be either due to nutritional causes, or increased phosphate loss in the urine whether FGF-23 mediated or not. XLH is FGF-23 mediated condition that resulted in phosphate wasting. Different mutations have been identified for XLH. Male and female are affected at a ratio of 1:2 with no male to male transmission but father can transmit it to his daughters. There are also Autosomal recessive DMP1, ENP1 mutations.[7-9]

Illustrative clinical cases

The session ended with illustrative clinical cases. Dr. Anya Rothenbuhler (France) presented a case of *1-a-hydroxylase deficiency* to illustrate dental abscesses are specific to XLH. Low phosphate in a calcipenic rickets patient can be due to high parathyroid hormone (PTH). Also 1, 25 Vitamin D assay is not invariably accurate and the normal range of 1, 25 Vitamin D in calcipenic rickets patients may not be true as they have high PTH and later is already converting all Vitamin D to active form. Suggested starting dose of 1 alpha Vitamin D 2–8 ug/day and maintenance of 1.5–3 ug/day, where the starting dose of 1, 25 Vitamin D 1–4 ug/day and maintenance of 0.75–1.5 ug/day. Patients with VDDR-1 will also be treated by Vitamin D (substrat) and calcium (age appropriate dose) during the 1st year. The presented case had CYP27B1, ch. 12 mutation which is autosomal recessive. Laboratory findings include hypocalcaemia, hypophosphatemia, high PTH and very low calciuria. Professor Agnès Linglart (France) and Dr. Volha Zhukouskaya (Italy) presented a case of *25-hydroxylase deficiency* who was treated by Dedrogyl (25 Vitamin D); 8 drops, each drop is 5 ug. Liver dysfunction is one of the causes of functional defect of 25 hydroxylation. The presented case was for a neonate who had transitional cholestasis that led to raised liver enzymes as well as dysfunction of 25 hydroxylase mechanism leading substantially to hypocalcemia. The 1, 25 Vitamin D in these cases is very sensitive and it degrades quickly.

Session 2: Presentation and diagnosis of X-linked hypophosphatemia

The afternoon session was dedicated for describing the clinical presentations and radiological diagnosis of XLH, clinical presentation of XLH in children, How to improve growth in XLH children and how to succeed in transition of care for XLH from childhood to adulthood and the final presentation focused on the management of pregnancy and newborns.

Clinical presentations of XLH were discussed by Professor Justine Bacchetta (France). Normal values of interest in XLH were presented including phosphate levels and TmP/glomerular filtration rate [Table 3]. A case of 5.5-year-old, short female with bowing of legs, growth retardation and dental caries, thought to have tyrosinemia was presented. Hepatomegaly with raised alpha-fetoprotein was noted. Hypophosphatemia was evident and thought to be related to the bowing of legs. Aims of treatment were discussed in similar cases; clinicians should not attempt to normalize the phosphate level, but rather to normalize serum alkaline phosphatase (ALP) and PTH levels and to ensure that no calciuria to be developed. A 3 monthly follow up was recommended. Use of Vitamin D analog in patients with normal renal function could lead to nephrocalcinosis; hence, this practice was discouraged. It was thought difficult or even impossible to correct the serum ALP according to personal observation from one of the colleagues. The expert suggested that if one wishes to check patients are they are taking alfacalcidol, measurement of 1, 25 Vitamin D level can be helpful. However, monitoring the adherence to phosphate therapy can be readily made by measuring urinary phosphate which will be high. Even changing from the conventional therapy can still be associated with high ALP. Burusomab use should continue until the closure of growth plates becomes evident. However, it may continue life-long. There is a limited experience with Cinacalcet in this condition. Adolescents with persistently high phosphate levels two times above the upper end of the normal range lead to tertiary hyperparathyroidism which may respond well to Cinacalcet as an off-label use, Haffnar commented.

Table 3: Normal values of interest in X-linked hypophosphatemia, phosphate levels, and TmP/glomerular filtration rate

Age groups	Phosphate level (mmol/L)	Age groups	TmP/GFR (mmol/L)
<3 months	1.55-2.4	Neonate	1.43-3.43
3-12 months	1.55-2.2	3 months	1.48-3.3
1-4 years	1.29-2.2	6 months	1.15-2.6
5-11 years	1.19-2.1		
12-18 years	1.1-1.9	2-15 years	1.15-2.44

GFR: Glomerular filtration rate

Radiological diagnosis of XLH was illustrated by Professor Catherine Adamsbaum, (France). She stressed the radiological ALADA principle, of using radiation "As Low As Diagnostically Acceptable". She then shed light on the metrics 3Ms when looking to the radiological images of patients with rickets (3Ms; Mineralization, morphology and modeling, and maturity of bones). In rickets, apoptosis of chondrocytes does not happen hence the epiphysis gets bigger. However, in XLH mineralization is preserved. Differential diagnosis of XLH from radiological point of view was discussed and that include (1) metaphyseal chondrodysplasia (Schmid disease), where there is widening of the growth plate and preserved mineralization but mild increase of height of the physis. (2) Blount disease, where there is developmental bowing but no increase in height of growth plates. (3) Hypophosphatasia, which is characterized by abnormal metaphysis but radiolucent, gives the "Tulip-like" image. Magnetic resonance imaging (MRI) can be a good model for imaging in XLH; it shows bone marrow abnormalities of the epiphysis and "Harris lines" - the thin transverse metaphyseal lines - which are related to the growth. Hence, MRI could provide good details for the XLH patients' follow up. No contrast is needed. EOS® imaging system; which is biplane X-ray imaging system using a technology based on the Nobel prize-winning work of physicist Georges Charpak on multiwire proportional chambers, characterized by (a) radiological images with less radiation, (b) reconstruction of three-dimensional model and (c) full length body imaging in standing position. Overall, it gives images with limited resolution, so it is good imaging model for follow up but not really for diagnosis of XLH. The discussion continues as it is known for XLH patients could have Chiari 1 malformation; so it was advised to look for syrinx that could be related to the impairment of the cerebrospinal fluid (CSF) circulation. Low cerebral tonsils would be considered when they are more than 5 mm below the foramen magnum. Interestingly, Vitamin C deficiency radiological features can be one of the differential diagnoses for XLH.

Special features for clinical presentation of XLH in children was elaborated by Dr. Anya Rothenbuhler (France), dental abscesses in healthy looking teeth is characteristic feature among XLH patients. A positive family history is present in 26% but *de novo* rickets 56%. Late diagnosis occurs in 12%. They have hyperlax joints. She noted that children will not develop limb deformities if they were diagnosed early. Less known features in XLH; Hearing loss due to abnormal mineralization of inner ear resembling otosclerosis also malformation of the skull and craniovertebral junction. If there is a family history of XLH that is transmitting in the family, therefore, it is advisable to do genetic testing for babies of these families at birth. Biochemical investigations to be arranged at 1 month of age, if normal repeat in 3 months, if normal repeat at 6 months – by then you should have the genetic testing results. Biochemical changes take some time to develop. For further reading, the clinical practice recommendations for the diagnosis and management of XLH can provide you with more detailed information.[10]

How to improve growth in XLH children was the theme of a presentation by Professor Dieter Haffner (Germany) who is the lead author of the latest evidence-based consensus guidelines.[10] In Denmark despite conventional therapy but their patients got shorter. Sitting height index is increasing as leg length is getting worse when the sitting height remained steady. How to improve growth in XLH children was the theme of a presentation by Professor Dieter Haffner (Germany) who is the lead author of the latest evidence-based consensus guidelines.[10] In Denmark despite conventional therapy but their patients got shorter. Sitting height index is increasing as leg length is getting worse when the sitting height remained steady. The progress in body disproportion is usually noted despite conventional treatment. Certainly, early conventional treatment improves growth in XLH patients; An experience from a single-center study, Toronto-Canada was shared during the presentation[11] Professor Haffner recommended to start the treatment within the first 6 months of life as that would lead to better results. Growth starts to deteriorate at 6–9 months of age in untreated patients with XLH. Data were presented showing the spontaneous growth in 127 XLH patients from Germany (collected in 1991 and 1992 from 49 paediatric centres). The mean height standard deviation score (SDS) in girls were −2.0, −1.9 and −2.1 and for boys they were −2.2, −1.6, and −3.0 for 3 different age groups, respectively; before the age of 1 year, between 1 and 5 years, and after the age of 5 years.[12]

Growth can be kept within the lower normal range by conventional treatment in the majority of patients. Large doses may promote growth but are associated with an increased risk of side effects. 64 week Burosumab treatment increased mean height by 0.19 SDS in XLH patients aged 4–12 years with prior conventional treatment. It did not result in catch-up growth but prevented early declines in growth in XLH patients aged 1–4 years with previous conventional treatment. Three-year growth hormone treatment increased mean height by 1.1 SDS in short prepubertal XLH patients with concomitant conventional treatment, but final height was not increased compared to control. So, it was suggested that if the growth hormone would be considered by the treating clinician, then perhaps it is better to be given early in the prepuberty period rather than during puberty. Although, he stressed that it is not

the routine recommendation to start growth hormone for all XLH patients.

The transition of patients care of XLH from childhood to adulthood and how best to succeed in transition was addressed by Dr. Raja Padidela from the (UK). He started by sharing the results of a study on the relative burden of disease at various stages of life. Taking conventional therapy was most "annoying" to children, growth becomes a concern during adolescence, whereas later on in life, fractures and need for pain and need for corrective surgery operations become the major issue for adults. Moving patients from paediatrics to adults like moving from the pond into the sea. Dr. Padidela emphasized the importance of CQC transition document that promotes "ready steady go" approach for transitioning service. Symptomatology of XLH can be shared between pediatrics and adults, for example, short stature, deformity of weight bearing limbs, teeth abscesses, excessive dental caries, osteomalacia, bone and joint pain, joint stiffness, muscle pain and weakness, Chiari malformation, gait abnormalities and diminished quality of life (QoL) including psychological impact. However, there are some features which are more apparent in pediatrics such as rickets, craniosynostosis, delayed and disproportionate growth, delayed motor development and gait abnormalities. Other evident symptoms for adults with XLH include fractures (including insufficiency fractures and looser zones), osteoarthritis, extraosseous calcification (including enthesophytes, enthesopathy, and spinal stenosis), hearing loss and disability that impacts ability to work. The goals of XLH treatment were reiterated as to (a) compensate for hypophosphatemia and low to low-normal 1, 25 Vitamin D levels that result from increased FGF-23 level, (b) improve the progressive bowing, anteromedial rotational torsion of tibiae and short stature in growing children, (c) to reduce the risk of dental and periodontal defects, (d) to reduce the need for surgical intervention, and (e) to screen for neurosurgical complications of XLH. Hence, to improve the outcomes, children should be diagnosed and treated as early as possible. Successful conventional treatment should not aim to normalize the serum phosphate as aiming to do so may result in overtreatment and secondary hyperparathyroidism. ALP is a useful biomarker for skeletal response. Blood PTH, ALP and calcium levels with urinary calcium creatinine ratio were suggested as useful biomarkers for efficacy and safety assessment. They should be measured every 3 months in infancy, every 3–6 months in childhood, every 3 months during puberty, and every year or 6 months if on treatment for adults. The renal ultrasound for nephrocalcinosis is to be done every year. There are some challenges to be addressed during adolescence; it is important for this cohort of patients to understand their disease, adhere to the treatment to prevent the complications. There should be some motivation for the treatment. Of course, support from family, friends, and school is of great value. In regards of XLH management in adults; usually, no treatment is required for asymptomatic adults with XLH. It is important to manage Vitamin D deficiency. Treating symptomatic adults by giving oral phosphorus 750–1600 mg daily, calcitriol 0.5–0.75 ug daily, or alfacalcidol 0.75–1.5ug daily.

The final presentation focused on the management of pregnancy and newborns. Professor Agnès Linglart (France) revised the physiology and changes happen during pregnancy as total calcium is usually at lower levels (2.0–2.2 mmol/L) due to hypoalbuminemia. Whereas, ionized calcium remain the same. Calciuria can be present and increased due to hyperfiltration. Interestingly 1, 25 Vitamin D increases by 2–3 folds by the end of pregnancy (200 pmol/L). PTH is normally lower but the PTH related protein is higher than usual.

Session 3: Burden of disease

The morning session of the second day started by reviewing the endocrine features in adults, Vitamin D in XLH and other rickets, rheumatological complications, neurosurgical complications of rickets, dental features in XLH and other rickets and the ear, nose and throat (ENT) features in XLH and management. Dr. Peter Kamenicky reviewed the complications of hypophosphatemic rickets. He highlighted the fact that in XLH; hyperparathyroidism is linked to long-term phosphate supplementation. On the other side, untreated patients who have hypophophatemia and high FGF23 would have suppressed PTH. Prevention, diagnosis and treatment of hyperparathyroidism is crucial for clinical management of XLH patients as the hyperparathyroidism can increase the risk of renal and bone complications. The exact prevalence of hyperparathyroidism in adults with genetic hypophosphatemia is not known as large studies are lacking. Creatinine clearance was found higher in hypophosphatemic patients. Hypercalcemic hyperparathyroidism is a likely result of PHEX mutation – nephrocalcinosis was reported. Young-onset hypercalcemic hyperparathyroidism can be effectively and safely cured by surgical resection. PTH adenoma and chief cells' hyperplasia occur more often, but adenomatous hyperplasia and oncocystic adenoma were also reported. The metabolic effect of raised FGF-23 (similar structure to FGF-19 and 21) is increasing of fat mass, large waist circumference, and lipid metabolism defect. Glucose metabolism in genetic hypophosphatemia is not normally affected – no association with diabetes or insulin resistance. Raised FGF23 induces left ventricular hypertrophy. It was suggested that cardiac MRI is more suitable for assessment of cardiac condition rather than echocardiogram because of deformities of the thoracic cage.[13]

Professor Wolfgang Hogler addressed the current challenges in nutritional rickets as he thinks it is a socioeconomic problem. Migration and global public health, policy and politics are the major challenges for effective prevention. He believes that the burden of the disease is mainly caused by ethnicity, culture, poverty, and geography. Those factors can result in low calcium diets, low sunshine exposure or inadequate sunshine exposure especially for the dark skin and poor public health standards. Nutritional rickets can lead to hypocalcemic seizures and tetany, hypocalcemic dilated cardiomyopathy, severe muscle

weakness, growth plate abnormality, osteomalacia, obstructed labor due to bone deformities and fractures, disability, low QoL, unemployment, and even mortality. The issues start early in life as Vitamin D of baby is 75% of his mum's level. Sufficient Vitamin D was considered when serum 25OHD is more than 50 nmol/L, insufficient when 30–50 nmol/L and deficient when it is <30 nmol/L. The recommended calcium intake for 0–6 months' infants is 200 and 260 mg/day for 6–12 months' infants. The daily calcium intake otherwise for other age groups is sufficient when it is more than 500 mg, insufficient 300–500 mg, and deficient when it is <300 mg/day. It was proposed to supplement Vitamin D to all infants in their 1st year of life (minimum 400 IU/day; independent of mode of feeding), all pregnant women, and all ethnic risk groups (minimum 600 IU/day). It was recommended to have national Vitamin D supplementation policies to incorporate universal supplementation policies regardless of the mode of feeding, monitor adherence at recommended childcare visits, and provide family financial support. Fortification of food was discussed; it can prevent rickets and improve Vitamin D status if appropriate food was used, sufficient fortification was used, supported by relevant legislation, adequate monitoring of the process, and indigenous food sources of calcium are promoted and subsidized.

Rheumatology complications were then discussed by Dr. Karin Briot (France). Indeed, the emphasis was on the impaired QoL. Various QoL scoring system in adults were presented such a HAQ, RAPID 3, short form (SF)-36 physical component score (PCS) and VAS pain score all of which can help in assessing the degree of impairment. Altered QoL was defined by HAQ >0.5, RAPID 3 >6 or SF-36 (one domain PCS or mental component summary > median). She confirmed that recognized risk factors for altered QoL include age, female gender, fatigue, and enthesopathies.

Neurosurgical complications of rickets were reviewed by Professor Federico Di Rocco (France). Sagittal suture loss seem to be the main type of craniosynostosis seen in XLH (59% will have complete or partial suture loss). Synostosis also seen in pseudohypoparathyroidism, osteopetrosis, and hypophosphatasia. The outcome of syringomyelia in XLH can be improved by improving the CSF circulation. This can be achieved by surgical intervention. XLH patients ought to be seen regularly by the neurosurgeon, regularly evaluated the surgeon can decide on who needs surgery; usually only <10% who would get operated. Fundus examination from year 1 is essential to roll out papilloedema; if fundus is normal; further imaging can be delayed.

Professor Catherine Chaussain (France) discussed the dental features in XLH patients. The hypophosphatemia directly affects the tooth structure. Children and adolescents are prone to multiple dental infections. Spontaneous dental necrosis with severe abscesses on deciduous and permanent teeth was noted in XLH. For necrosis and cellulitis, biantibiotic therapy as first line is recommended (metronidazole and amoxicillin if no allergy). Periodontitis occurs usually at the age of 40s, particularly in diabetic patients. However, XLH patients are more susceptible and they ever start having it even in their third decade. There is some cementum; so, it is unlike hypophosphatasia there will be no spontaneous tooth loss. Patients with XLH could have normal enamel but thin with cracks, dentin hypodensity or hypomineralization with unmerged calcospherites, enlarged pulp chambers. Children with XLH should have regular follow-up (every 3–6 months); they should be monitored and managed the spontaneous abscesses. Sealing the pits and fissures with resins on temporary and permanent molars is recommended. Rigorous systemic treatment of XLH improves dental health. Prof. Chaussain has asked insurance companies to include oral care and orthodontic treatment under the provided cover. The ENT features in XLH and management were covered by Dr. Jérôme Nevoux (France).

Session 4: Practical management of X-linked hypophosphatemia

The practical aspects of managing XLH included initiation, adjustments and outcomes of conventional therapy were outlines by Dr. Anya Rothenbuhler (France). Limiting the effect of FGF-23 in treatment of XLH was covered by Professor Agnès Linglart (France) and Dr. Volha Zhukouskaya (Italy). Expectations of patients were given by Dr. Pol Harvengt (Belgium). Following the state of the art management, the principles were applied on 4 clinical cases with suspected or confirmed XLH.

It was recommended for patients aged 5 years and older to have hearing assessment and musculoskeletal function assessment (gait). All patients otherwise including those younger than 5 years old, to have growth charts, bone deformities and signs of rickets to be reviewed, measurement of intermalleolar distance and intercondylar distance, head circumference and skull shape to be assessed, neurological examination (consequences of craniosynostosis and spinal stenosis) to be reviewed and to have dental and oral examination as part of the workup.

It was underscored that the objectives of treating XLH in children are healing or preventing rickets and reducing pain, improving or correcting leg deformities, improving the musculoskeletal function, increasing the growth velocity to improve the final height, avoiding treatment-related complications, and preventing adult rheumatological complications. There should be a transitioning of care service. It was emphasized that improvement of the patients' QoL is very important.

The standard therapy strategy of managing XLH, otherwise known as conventional therapy is based on compensating the renal defects, by giving Vitamin D analogs and phosphate supplements. That ideally should help in healing the rickets, mineralization and growth. Clinicians should be cautious and careful when they treat XLH, Vitamin D analogs can lead to the development of hypercalciuria that subsequently could lead to nephrocalcinosis. Phosphate therapy can lead to

hyperparathyroidism. So, the treating physicians should be carefully monitoring the development of hypercalciuria and hyperparathyroidism.

Three important rules were reiterated. First, do not aim for correcting the hypophosphatemia, (2) regular adjustments (every 3 months) for efficacy and toxicity, and third, giving the phosphate supplement in divided doses.

ALP usually get normalized within 1 year of starting the conventional therapy. Leg bowing correction (1 cm/6 months) and restoring the optimal growth should be achieved within 2–3 years. The initial dose of elemental phosphorus for infants or preschool children is 20–60 mg/kg/day, adjusted according to improvement of rickets, growth, ALP, and PTH levels. Young patients who have high ALP level will need frequent administration of phosphate (4–6 times/day, lowered to 3–4 times/day when ALP is normalized). The dose can be increased if progressive disease but it should not exceed 80 mg/kg/day to prevent gastrointestinal discomfort and hyperparathyroidism. Consider low dose in milder phenotypes (e.g., infants diagnosed by family screening).

Burosumab is monoclonal antibody to treat XLH with radiographic evidence of bone disease in children of 1 year of age and older. It was shared by the speakers that in France, it is given based on these conditions: (a) approval by a reference center expert in rare bone and mineral diseases, (b) children with complication of the conventional therapy, (c) children with severe disease, or (d) children with late diagnosis. Burosumab is given subcutaneously every 2 weeks.

Session 5: Management of X-linked hypophosphatemia: Clinical cases from the Gulf

The last session of the program was dedicated to discussion of the preceptorship focused on the challenges and special needs for XLH patients in the Arabian Gulf region and was moderated by the host expert. The discussion considered the various types of hypophosphatemic disorder seen in the region, available resources for diagnostic testing, building capacity for collaboration between all concerned specialties and how best to identify the right type of adult specialists to allow a seamless transition. For-most part, adult endocrinology seemed the most appropriate specialty to undertake this role. Concerns about medical insurance coverage were discussed and experiences were shared among delegates from various countries. Perhaps, most importantly was the discussion on how best to identify such patients who may be suffering from this rare condition. Potential low awareness of physicians of XLH was raised. Reportedly, a survey of the physicians' perceptions and practices in identification and management of rare genetic and metabolic bone disorders is ongoing; narrative review of the literature from the Middle East and North Africa is also being contemplated. Furthermore, a Gulf-dedicated guidance statement, with educational slide deck is also being developed by a group of experts, it was revealed. At the end of the day, the delegates were escorted by the host to visit the rare diseases unit in the hospital to identify the various clinical, epidemiological and laboratory resources and ongoing research projects. With its long track record, the unit was obviously very equipped with [Figure 2].

Figure 2: The Bicetre Paris Sud Hospital, France where the event took place

Final Remarks

The preceptorship was a high quality, in depth review of the subjects of rare metabolic and genetic bone diseases. In summary, phosphate is a cornerstone of several physiological pathways including skeletal development, bone mineralization, membrane composition, nucleotide structure, maintenance of plasma pH, and cellular signaling. The kidneys have a key role in phosphate homeostasis with three hormones having important functions in renal phosphate handling or intestinal absorption namely, PTH, FGF-23, and 1, 25(OH) 2D. FGF-23 is a direct phosphaturic factor that also inhibits 1, 25(OH) 2D and PTH. FGF-23 also has effects on the cardiovascular, immune, and central nervous systems. Genetic diseases may affect the FGF-23 pathway, resulting in either increased FGF-23 levels leading to hypophosphatemia or defective secretion/action of intact FGF-23 inducing hyperphosphatemia. Understanding the biochemical and physiological background of such disorders sharpens the focus of physicians' diagnostic and therapeutic abilities.

The content was undoubtedly superb, and the faculty members were world class. The selection of the delegates was fairly appropriate by selecting academics and practicing clinicians involved in the care of rare genetic and metabolic disorders or those with an interest in research and education in the area. From an organization point of view, few issues could have been conducted in a better manner. For instance, with such a heavy curriculum and specialized group, abstracts or outlines of the presentations could have been made available in a booklet for the delegates. Furthermore, an audience participation system with fully interactive sessions would have been valuable and encouraging more focus. Accommodation could have also been nearer to the venue of the lectures to waste less time in transportation to and from the meeting venue. Finally, with such"star-studded" meeting, a high quality clear audio recording of

the lectures could have been used to produce a valuable and unique set of educational videos to be made available elsewhere.

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Authors' contribution

Equal contribution in perception of the idea, drafting and finalizing the report.

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Conflicts of interest

This report was solicited by the editorial board of Ibnosina Journal of Medicine and Biomedical Sciences. It was not commissioned by the sponsor of the event who had no access to it before publication.

Compliance with ethics principles

Not applicable.

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