CLINICAL QUIZ (p85-86) ANSWER

What is the diagnosis?

The boy presented with macrocephaly, short stature, bowlegs, radial and ulnar metaphseal spraying and hypophosphatemia. The clinical features were compatible with hypophosphatemic rickets. In view of maternal history of short stature, X-linked dominant hypophosphatemic rickets / X-linked hypophosphatemia (XLH) (OMIM#307800) and autosomal dominant hypophosphatemic rickets / autosomal dominant hypophosphatemia (ADH) (OMIM#193100) were our top differentials.

Sequence analysis for coding exons of the *PHEX* (OMIM*300550) gene showed a hemizygous nonsense c.1104G>A (p.Trp368*) mutation in exon 10 of the *PHEX* gene. The variant was not detected in maternal blood. It was a de novo condition. The diagnosis of XLH (OMIM#307800) was substantiated.

The phenotypic spectrum of XLH varies from isolated hypophosphatemia to severe lower limbs bowing. It frequently manifests in the first two years of life, when weight bearing period starts, as bowing of lower limbs, delayed walking, abnormal gait or growth stunting.[1] Our patient had the height centile drifting away from birth to below third at around 2.5 years old. He experienced mild leg bowing at 2 years old. The disease may be initially misdiagnosed for vitamin D deficiency, but biochemical investigations revealing lack of response to vitamin D supplements (vitamin D resistant) usually allows the diagnosis. X-ray demonstrates typical features of rickets without significant bone resorption (as opposed to vitamin D deficiency rickets).

The prevalence of XLH is estimated between 1.2-3.0/60,000.[2,3] The clinical manifestation is variable. Thus under-diagnosis is not uncommon.[4] Despite a wide degree of clinical variability, penetrance is approaching 100% by age one year[5] There is no known difference between penetrance in males and females.

What are the clinical features of XLH?

XLH affected individuals would experience a diverse range of medical problems. At the time of diagnosis, they may experience delayed and disproportionate growth, lower extremity bowing, rickets, and cranial abnormalities and delayed motor development / gait problem. Individuals appear disproportionate with leg length SD score being significantly lower than sitting height SD score. Genu varum or genu valgus can occur while torsion and rotation of lower extremity may occur sometimes. Rickets features, e.g. wrist swelling, rachitic rosary, swollen knees, craniotabes, Harrison's sulci and bone pain would be found in affected individuals. In children, X-ray would reveal widened / frayed / cupped metaphysis and sometimes beading of ribs suggesting poor skeletal mineralisation leading to overgrowth of costochondral joint cartilage. Cranial abnormalities, e.g. frontal bossing, craniosynostosis, and Chiari malformations were reported in some patients with XLH but the exact incidence is unknown. The delayed motor development and gait problem are mainly contributed by lower limb bowing.

When they grow older, they may experience dental abnormalities, joint pain and impairment mobility, muscle pain or weakness, osteomalacia and stress fracture and hearing difficulties. Individuals with XLH are prone to spontaneous dental abscesses which are due to change in the dentin component of teeth. In adults, enthesopathy (calcification of the tendons, ligaments, and joint capsules) associated with joint pain and impaired mobility are common complaints. Sensorineural hearing loss has been reported but the actual prevalence of hearing loss is not known. In some patients with affected hearing, radiological finding showed generalised osteosclerosis and thickening of the petrous bone. Adults with XLH have a significantly reduced final height with a standard deviation score (SDS) of -1.9 compared to reference standards.[4] Female and male with XLH have with similar clinical presentation.

What are the biochemical defects and molecular diagnosis of XLH?

XLH is a rare disease caused by mutations in the *Phosphate Regulating Endopeptidase Homolog, X-linked* (*PHEX)* gene. The *PHEX* gene is located on chromosome Xp22.11. This endopeptidase is primarily expressed on the surface of osteoblast, osteocytes, odontoblasts and cementoblasts. This endopeptidase regulates osteogenic cell differentiation and bone mineralisation. The pathophysiology of XLH is complex and it involves different molecular pathways that variously contribute to different manifestations of the disease. One important molecular pathway is that the inactivating mutation in *PHEX* gene will result in elevated level of fibroblast growth factor 23 (FGF23). FGF23 elevation contributes to hypophosphatemia by limiting intestinal phosphate absorption through restricting active vitamin D (1,25 (OH)2 vitamin D) response to hypophosphatemia and increasing urinary phosphate excretion by downregulating renal sodium-phosphate transporters (Figure 2).

Thus, at the time of diagnosis, patients show low serum phosphate levels secondary to increased phosphaturia (reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR)). The normal physiologic response to hypophosphatemia of an elevation of 1,25 (OH)2 vitamin D is absent. Usually, serum calcium and 25-hydroxy vitamin D are within the normal range while parathyroid hormone is normal to slightly elevated. At childhood period, Alkaline phosphatase is characteristically elevated, especially during time of rapid growth, and would returns to normal in adulthood with or without treatment.

Among the individuals with genetically confirmed XLH, around 70% is related to sequence error in *PHEX* gene (small intragenic insertion / deletion, missense, nonsense and splice-site variant) detected by sequence analysis. The remaining 30% is related to (multi)exon or whole gene deletion detected by gene-targeted deletion / duplication analysis.[4] Studies showed truncating variants or pathogenic variants in the C-terminal portion of *PHEX* would have

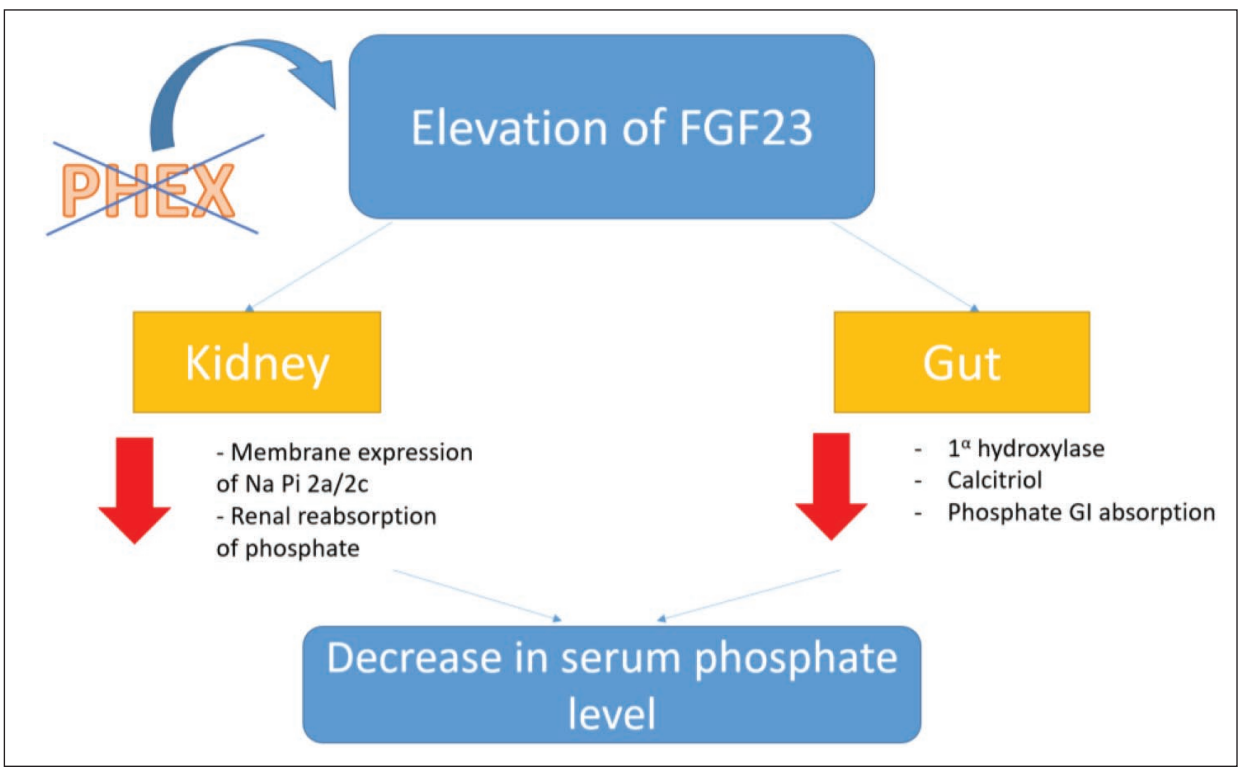

Figure 2 Showing the mechanism of inactivating mutation in *PHEX* gene effect on FGF23.

more severe bone disease (severe bowing of lower limbs and the need for surgery).[5,6] Patients with clearly pathogenic variants (e.g. nonsense variants, splice -site variants and frameshift variants) presented with lower tubular resorption of phosphate and lower 1, 25 (OH)2 vitamin D level than those with possible deleterious variants (missense variants and in-frame deletion).[7]

Genetic counseling and management of XLH individuals

XLH shows an X-linked dominant inheritance pattern. The mother of a proband may be affected (heterozygote) or the affected individual may have a de novo pathogenic variant. If the mother of the proband carries an *PHEX* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. An affected male passes the pathogenic variant to all his daughters and none of his sons. The features of X-linked hypophosphatemia are similar in males and females. Due to great intrafamilial variation, severity cannot be predicted.

Management of XLH syndrome takes multi-disciplinary approach involving pediatricians, endocrinologists, radiologists, orthopedic surgeons, dental surgeons, clinical geneticists, ENT surgeons ...etc. After the diagnosis is established, management mainly focus on three aspects: pharmacological and surgical treatment, prevention of secondary manifestations and surveillance.

Pharmacological treatment focuses on pain alleviation and correcting bone deformation. In children, treatment usually starts at the time of diagnosis and continues till long bone growth is completed. Treatment includes oral phosphates and high dose calcitriol (active form of vitamin D). Titration is needed to avoid gastrointestinal side effects like diarrhea. Doses are adjusted based on successful reduction of serum alkaline phosphatase, improvement in lower limbs bowing, radiological improvement e.g. resolution of rachitic changes and improved growth velocity while balancing the occurrence of secondary complications at the same time. In adults, treatment is generally reserved for individuals with symptoms like skeletal pain, upcoming orthopedic surgery, biochemical evidence of osteomalacia with an elevated alkaline phosphatase, or recurrent stress fractures.[8]

Despite adequate pharmacologic therapy, some individuals with XLH would still have persistent lower-limb bowing and torsion, which may lead to misalignment of the lower extremity. In these individuals, surgical treatment is frequently pursued. Surgical options are age-dependent. For degenerative joint disease and enthesopathy, total hip and knee arthroplasty is sometimes required.

Individuals with XLH are prone to recurrent dental abscesses leading to premature loss of decidual and permanent teeth. Good oral hygiene with flossing and regular dental care and fluoride treatments are essential for prevention. A recent study has showed that treatment of adults with phosphate and calcitriol can improve the severity of dental disease.[9]

For prevention of secondary complications, hyperparathyroidism is associated with treatment for XLH. Hyperparathyroidism most often occurs secondary to high phosphate doses and may proceed to tertiary hyperparathyroidism (hypertrophied and uncontrolled parathyroid gland). If secondary hyperparathyroidism is detected, either the calcitriol dose may be increased or the phosphate dose decreased. If tertiary hyperparathyroidism is identified, surgical evaluation is needed.

Hypercalcaemia and hypercalciuria are complications of long-term treatment for XLH. They are associated with high calcitriol doses. If hypercalcaemia or hypercalciuria is detected, the calcitriol dose should be decreased. Nephrocalcinosis is reported in persons medically treated for XLH. It can occur despite absence of laboratory detected hypercalcaemia and hypercalciuria. A baseline renal ultrasound examination is recommended before start of treatment. The frequency of renal ultrasound examination to monitor for the development of nephrocalcinosis is not established; one- to five-year intervals have been recommended [Carpenter et al 2011, Sabbagh et al 2014].

Surveillance would be indicated for disease progression, treatment response and therapeutic complication. In order to monitor for hyperparathyroidism, hypercalciuria and hypercalcaemia, intact parathyroid hormone, alkaline

phosphatase level, serum calcium concentrations, urinary calcium, phosphate and creatinine should be measured quarterly. Lower extremity X-ray is needed for assessing skeletal response to treatment while frequency is guided by physical examination and symptoms. Renal ultrasound examination is needed to monitor nephrocalcinosis. Dental follow up is recommended twice yearly for children or teenagers with XLH and at risk for caries.

Acknowledgement

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References

1. Whyte MP, Schranck FW, Armamento-Villareal R. X-linked hypophosphatemia: a search for gender, race, anticipation, or parent of origin effects on disease expression in children. J Clin Endocrinol Metab 1996;81:4075-80.
2. Endo I, Fukumoto S, Ozono K, Namba N, Inoue D, Okazaki R, et al. Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment. Endocr J 2015;62:811-6.
3. Rafaelsen S, Johansson S, Raeder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. Eur J Endocrinol 2016;174:125-36.
4. Mary DR. X-linked hypophosphatemia. GeneReviews [internet]. 2017 April [cited 2020 July31]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK83985/
5. Holm IA, Nelson AE, Robinson BG, Mason RS, Marsh DJ, Carpenter TO. Mutational analysis and genotype-phenotype correlation of the PHEX gene in X-linked hypophosphatemic rickets. J Clin Endocrinol Metab 2001;86:3889-99.
6. Song HR, Park JW, Cho DY, Yang JH, Yoon HR, Jung SC. PHEX gene mutations and genotype-phenotype analysis of Korean patients with hypophosphatemic rickets. J Korean Med Sci 2007;22:981-6.
7. Morey M, Castro-Feijóo L, Barreiro J, et al. Genetic diagnosis of X-linked dominant hypophosphatemic rickets in a cohort study: tubular reabsorption of phosphate and 1,25(OH)2D serum levels are associated with PHEX mutation type. BMC Med Genet 2011;12:116.
8. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res 2011;26:1381-8.
9. Connor J, Olear EA, Insogna KL, et al. Conventional Therapy in Adults With X-Linked Hypophosphatemia: Effects on Enthesopathy and Dental Disease. J Clin Endocrinol Metab 2015;100:3625-32.