SAT-360

Title: Out of Sight, Out of Mind: PHEX 3'-UTR c.*231A>G X-Linked Hypophosphatemia in Adults: A Case Study of One Family Pedigree with a Widely Variable Phenotype

X-linked hypophosphatemia (XLH) is an inherited form of hypophosphatemia that is part of a group of disorders that leads to impaired bone mineralization, which can manifest as rickets in children and osteomalacia in adults. Mutations in PHEX, DMP1, ENPP1, and activating mutations in FGF23 have each been shown as genetic causes for XLH. PHEX is a zinc metallopeptidase which reduces expression of FGF23 through mechanisms that are not fully understood. Inactivating mutations in the PHEX gene cause elevated levels of FGF23, resulting in renal phosphate-wasting, impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and impaired bone mineralization with osteomalacia. Though the clinical significance of FGF23 levels is not clearly understood, it has also been shown that FG23 increases with age.

XLH has a reported prevalence of 3.9–5 per 100,000. We speculate that this may be under recognized and that diagnosis may be delayed for many years in those with mild forms of XLH due to non-specific symptoms. Diagnosis may be complicated by normal or low-normal serum phosphorus levels. Adults may be mistakenly diagnosed with ankylosing spondylitis, polyarthritis, osteoarthritis, diffuse idiopathic skeletal hyperostosis and other disorders that cause stiffness. Some clinical manifestations of XLH in adults include dental disease, skeletal and spinal disease, sensorineural hearing loss, kidney stones, renal impairment, and hyperparathyroidism. The PHEX 3'-UTR c.231A>G near the polyadenylation signal has been previously described to cause milder severity in men and seemingly unaffecting women, but data for comparison is limited.

We present a large, multigenerational family with a mutation in the PHEX gene (3'-UTR c.*231A>G) demonstrating variable penetrance in the pedigree. Of the members positive for the mutation, the most common symptoms were sensorineural hearing loss, enthesopathy, and dental disease. Most had normal or low-normal phosphorus levels in both genders. Two patients had prior diagnoses of ankylosing spondylitis/seronegative spondyloarthropathy. In general, males with the mutation had more severe symptoms than females. However, females with a severe phenotype and low phosphorus was also observed. The disease burden was cumulative over time and correlated with serum phosphorus levels. Musculoskeletal symptoms were increased in the members over the age of 60.

Sources:

Chesher, Douglas et al. Outcome of Adult Patients with X-Linked Hypophosphatemia Caused by PHEX Gene Mutations. Vol. 41. Dordrecht: Springer Netherlands, 2018. Web.

Zhang, Cong et al. Clinical and Genetic Analysis in a Large Chinese Cohort of Patients with X-Linked Hypophosphatemia. Vol. 121. Elsevier Inc, 2019. Web.

Bone and Mineral Metabolism

NEW FRONTIERS IN BONE AND MINERAL METABOLISM

Long-Term Safety in Adults with X-Linked Hypophosphatemia (XLH) Treated with Burosumab, a Fully Human Monoclonal Antibody Against FGF23: Final Results of a Phase 3 Trial

Farzana Perwad, MD[1], Anthony A. Portale, MD[2], Thomas O. Carpenter, MD[3], Karine Briot, MD[4], Erik Allen Imel, MD[5], Peter Kamenicky, MD[6], Thomas Joseph Weber, MD[7], Pisit Pitukcheewanont, MD[8], Hae Il Cheong, MD[9], Suzanne Marie Jan De Beur, MD[10], Yasuo Imanishi, M.D., Ph.D.[11], Nobuaki Ito, MD[12], Robin Lachmann, MD[13], Hiroyuki Tanaka, MD,PHD[14], Lin Zhang, PhD[15], Alison Skrinar, PhD[16], Linda Rees, MBChB[15], Karl Leonard Insogna, MD[17].

[1]University of California San Francisco, San Francisco, CA, USA, [2]Univ of CA - San Francisco, San Francisco, CA, USA, [3]Yale Univ Schl of Med, New Haven, CT, USA, [4]Centre d'Evaluation des Maladies Osseuses, Hôpital Cochin, Paris, France, [5]IN Univ School of Med, Indianapolis, IN, USA, [6]Université Paris-Sud, Le Kremlin Bicêtre, Paris, France, [7]Duke University, Durham, NC, USA, [8]Children's Hospital Los Angeles, Los Angeles, CA, USA, [9]Seoul National University Children's Hospital, Seoul, Korea, Republic of, [10]Johns Hopkins Univ Sch of Med, Baltimore, MD, USA, [11]Osaka City University Graduate School of Medicine, Osaka, Japan, [12]The University of Tokyo Hospital, Tokyo, Japan, [13]University College London Hospitals, London, United Kingdom, [14]Okayama Saiseikai Gen Hosp, Okayama City, Japan, [15]Ultragenyx Pharmaceutical Inc., Novato, CA, USA, [16]Ultragenyx Pharmacutical Inc, Novato, CA, USA, [17]Yale Univ/Sch of Med, New Haven, CT, USA.

OR29-01

Burosumab, a fully human IgG1 monoclonal antibody to FGF23, is approved in Canada and Brazil to treat XLH in patients ≥1 year of age and in the US to treat XLH in patients ≥6 months of age. Burosumab has also received conditional marketing authorization in Europe to treat XLH with radiographic evidence of bone disease in children ≥1 year of age and in adolescents with growing skeletons. Burosumab significantly improved serum phosphorus, fracture/pseudofracture healing, stiffness, and physical functioning in a phase 3, double-blind, multicenter study (CL303, NCT02526160). In this trial, subjects were randomized 1:1 to receive burosumab or placebo subcutaneously every 4 weeks. At Week 24, subjects in the placebo group crossed over to receive burosumab (total duration ≥96 weeks). Here, we report final long-term safety results from this trial. Most (119/134, 89%) subjects completed 96 weeks and received 1 mg/kg burosumab; protocol-specified dose reductions were required for 11/134 (8.2%) subjects to effectively manage hyperphosphatemia (all mild [Grade 1]). Mean (±SE) baseline serum phosphorus was 1.98 (±0.03) mg/dL and was 2.97 (±0.05) mg/dL at Week 94 (midpoint of dose interval). Mean (±SE) iPTH level was 96 (±3.8) pg/mL at baseline and progressively declined to 79 (±3.3) pg/mL at Week 96. Nephrocalcinosis score at Week 96 changed by 0 in 101 subjects, -1 in 9 subjects, +1 in 10 subjects (14 subjects not available). There were no meaningful changes in ectopic

mineralization. There were no neutralizing antibodies. No treatment-emergent adverse events led to study or treatment withdrawal. Serum phosphorus was maintained with long-term burosumab treatment, with no evidence of loss of effect in adults with XLH. Burosumab dose reductions effectively managed mild hyperphosphatemia. Frequency, severity, and types of AEs reported were consistent with previous burosumab trials.

Thyroid

THYROID DISORDERS CASE REPORTS I

Use of Plasmapheresis for Treatment of Thyroid Storm Resistant to Antithyroidals

Myrian Noella Vinan Vega, MD[1], Ana Marcella Rivas Mejia, MD[2], Kenneth Nugent, MD[1].
[1]TEXAS TECH HEALTH SCIENCE CENTER, LUBBOCK, TX, USA, [2]Texas Tech Univ Hlth Sci Ctr, Lubbock, TX, USA.

SUN-515

Management strategies of thyroid storm include measures to reduce thyroid hormone synthesis, hormone release, conversion from T4 to T3, and inhibition of the peripheral effects of excessive thyroid hormone. Plasmapheresis has been described as a treatment option when traditional therapy is not successful or not feasible.

We present a case of an adult patient who presented in thyroid storm in whom plasmapheresis was used successfully as a bridge to thyroidectomy.

51-year-old female with history of hypertension presented with sudden onset shortness of breath, and palpitations. She had an irregular heart rate of 140BPM, respiratory rate of 40, mean arterial blood pressure 65mmHg. Electrocardiogram confirmed atrial fibrillation with rapid ventricular response and the patient was admitted to the intensive care unit. She was started on diltiazem drip and subsequently received amiodarone and electrical cardioversion due to persistent rapid heart rate. She developed respiratory distress and required endotracheal intubation.

Initial thyroid profile revealed low TSH and normal FreeT4, but her FT4 increased above normal on day 2, treatment for thyroid storm was initiated with potassium iodine, hydrocortisone and propylthiouracil. She was kept on propranolol 80 mg q/4h, intravenous esmolol 50 mcg/kg/min, diltiazem drip 5 mg/hr, and was started on Digoxin 0.25 mg q/4h. TSI and TPO were undetectable, and thyroid ultrasound revealed a right nodule measuring 5 x 2.2 x 3.7cm. Thyroid storm was attributed to a toxic nodule exacerbated by exposure to excess iodine (contrast for imaging and amiodarone). Propylthiouracil, hydrocortisone and beta blocker were maximized, and cholestyramine was added, but their heart rate remained elevated, blood pressure worsened requiring synchronized cardioversion.

Because of persistent hyperthyroid state, refractory to medical treatment, patient was started on plasmapheresis on day 10 of hospitalization, she underwent 5 sessions with significant reduction in Free T3 and Free T4 (Figure 1), and remarkable improvement in her hemodynamic status and resolution of tachycardia. Patient underwent total thyroidectomy on day 16, without complications.

Plasmapheresis has been described as a treatment option for refractory thyroid storm, as a bridge therapy prior thyroidectomy. During plasmapheresis, thyroid-binding globulin, thyroid hormones, cytokines and putative antibodies are removed with the plasma; then the colloid replacement provides new binding sites for circulating free thyroid hormone (2). Although albumin binds thyroid hormone less avidly than TBG, it provides a much larger capacity for low-affinity binding that may contribute to lower free thyroid hormone levels, providing a window for thyroidectomy.

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Muller C et al, Role of Plasma Exchange in the Thyroid Storm, Therapeutic Apheresis and Dialysis15 (6): 522–531

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS I

Identification of Heterozygous LRP5 Mutation and a TGFβ-1 Variant of Unknown Significance in a Patient with Hearing Loss, High Bone Mass, and Oropharyngeal Exostoses

Cheng Cheng, MD[1], James Avery, MD[1], Gary Gottesman, MD[2], Steven Mumm, PhD[3], Michael P. Whyte, MD[2].
[1]WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, St Louis, MO, USA, [2]Shriners Hospital for Children, Saint Louis, MO, USA, [3]BARNES JEWISH HOSPITAL, Saint Louis, MO, USA.

SAT-384

Background: Manifestations of the high bone mass (HBM) disorders not only include strong bones, but also excessive bones causing cranial nerve palsies and oropharyngeal exostoses. Due to overlap of clinical phenotype in dense bone diseases, one or more distinct genes may be involved. Up-regulation in bone formation can result from gain of function mutation of the low-density lipoprotein receptor-related protein 5 (LRP5), which mediates activation of the canonical Wnt pathway via co-binding with the frizzled protein, but may also be a consequence of activating mutations in the transforming growth factor β1 (TGFβ-1) gene that associate with stimulated osteogenesis. **Clinical Case:** Here we report a 41 year-old woman referred for incidentally found dense bones on screening dual-energy X-ray absorptiometry (DXA) that led to subsequent revelation of several family members sharing similar histories including inability to float in water, strong bones on skeletal surgery, and presence of palatal exostoses. Her childhood history included mandibular pain developing at age 15 years due to bony overgrowth of her lower jaw requiring multiple drilling for removal. At age 33, she manifested trigeminal neuralgia initially responsive to medical management but eventually needed microvascular decompression for unremitting pain. Preoperative brain magnetic resonance imaging (MRI) noted significant hyperostosis of the skull as well as mild narrowing of internal auditory canals, for which auditory testing showing mild mixed hearing loss in her right ear. Skeletal survey revealed diffuse thickening of axial and appendicular skeleton with characteristic endosteal hyperostosis. DXA demonstrated Z scores of +8.3 and +5.3 in the lumbar spine and total hip, respectively. Torus palatinus was also identified on exam. Mutational analysis disclosed a heterozygous LRP5 missense mutation, c.844A>G, p.Met282Val,