Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Hypophosphatemia Gene Panel Sponsored Program: A High Yield Of Molecular Diagnoses from Clinically Confirmed XLH and Suspected XLH/ Genetic Hypophosphatemia

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X-linked hypophosphatemia (XLH), an X-linked dominant disorder caused by a pathogenic change (variant) in the *PHEX* gene, affects males and females of all ages. Rickets and osteomalacia may be present along with short stature, lower limb deformity, muscle pain and/or weakness/fatigue, bone pain, joint pain/stiffness, hearing difficulty, enthesopathy, osteoarthritis and dental abscesses. Patients with XLH have below-normal serum phosphate and elevated serum FGF23. XLH is one of multiple etiologies of hypophosphatemia; depending on genetic cause, management may differ. The program provides a no-cost test to confirm a clinical XLH diagnosis or to aid diagnosis of suspected XLH or other genetic hypophosphatemia.

Methods Program eligibility criteria: >/=1y old and either clinical XLH diagnosis (*confirmatory*) or suspicion of XLH/ genetic hypophosphatemia (*suspected*) as evidenced by 2 or more clinical signs/ symptoms. The next generation sequencing gene panel includes 13 genes: *ALPL, CLCN5, CYP2R1, CYP27B1, DMP1, ENPP1, FAH, FAM20C, FGF23, FGFR1, PHEX, SLC34A3* and *VDR*. Copy number variant (CNV) detection was performed.

Results 317 unrelated probands have been tested as of October 2, 2019. Of 158 XLH confirmatory samples received, 143 (90.5%) had a *PHEX* variant: 14 (9.8%) were variants of uncertain significance (VUS) and 129 (90.2%) were either pathogenic or likely pathogenic (P/LP) XLH molecular diagnoses. Of the 15 patients (9.5%) where no *PHEX* variant was found, one had a P variant in *FGF23* (autosomal dominant hypophosphatemic rickets molecular diagnosis) and another had P and LP variants in *ENPP1* (autosomal recessive hypophosphatemic rickets Type 2 molecular diagnosis). Of 159 suspected samples, 101 (63.5%) had a *PHEX* variant: 14 (13.9%) were variants of uncertain significance (VUS) and 87 (86.1%) were P/LP (XLH molecular diagnoses). No *PHEX* variant was found for 58 (36.5%) of suspected samples; however, 5 of these had other findings: a dominant-negative heterozygous P variant for *ALPL* was detected in 3 samples (3 hypophosphatasia, HPP, molecular diagnoses); a fourth carried two P variants in *ALPL*; a fifth had a LP variant and a VUS in *ENPP1* (autosomal recessive hypophosphatemic rickets Type 2). Of 121 unique P/LP *PHEX* variants detected, 59 were deletions duplications or insertions. A complex rearrangement and an Alu-mediated insertion were detected in the full cohort. To date, additional family member testing was performed for 10 probands with original VUS: in 4 cases the VUS was reclassified to P/LP; 2 were reclassified to P/LP due to more clinical info, highlighting the value of family testing and clinical info to resolve VUS. RNA analyses to resolve VUS and unidentified variants may further improve molecular diagnoses of genetic hypophosphatemia. Program results demonstrate a high diagnostic yield for confirmatory and suspected XLH/ genetic hypophosphatemia.

Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Impact of Race and Obstructive Sleep Apnea on Glucose and Insulin Regulation in Women with PCOS

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The prevalence of prediabetes and diabetes is substantially higher in PCOS women with obstructive sleep apnea (OSA) compared to PCOS women without OSA[1,2,3]. Prior studies, however, did not examine the complex interaction between race and OSA on metabolic function in PCOS. We sought to determine if the impact of OSA on glucose and insulin metabolism is affected by race. We studied non-Hispanic white (NHW) (n=53) and African-American (AA) (n=48) women with PCOS. Following an overnight polysomnogram (PSG), PCOS women (NHW without OSA n=40; NHW with OSA n=13; AA without OSA n=36; AA with OSA n=12) had a 2-h 75-g oral glucose tolerance test (OGTT) with blood sampling every 30 minutes for measurement of glucose, insulin, and C-peptide concentrations. OSA severity was measured by the Apnea-Hypopnea Index (AHI). Only women without OSA (AHI < 5) or with moderate-to-severe OSA (AHI > 15) were included in these analyses; women with mild OSA were excluded. Insulin secretion rates (ISR) during the OGTT were derived by deconvolution of C-peptide levels [4]. Area under the curve (AUC) response to the glucose challenge was calculated using the trapezoidal method. BMI and age did not differ between races in PCOS women without OSA (BMI [kg/m^2]: 36.3±1.2 vs. 37.2±1.1, p=0.58; Age [yr]: 27.7±0.8 vs. 27.2±0.8, p=0.65; for NHW and AA respectively), or in PCOS women with OSA (BMI [kg/m^2]: 42.8±1.7 vs. 44.7±2.0, p=0.50; Age [yr]: 31.4±1.6 vs. 28.6±1.6, p=0.18; for NHW and AA respectively). OSA severity was similar in NHW and AA PCOS women without OSA (AHI: 1.5±0.2 vs 2.1±0.2, p=0.076), and PCOS women with OSA (AHI: 32.0±4.9 vs. 28.3±4.4, p=0.26). Higher glucose responses during the OGTT were observed in NHW PCOS women with OSA compared to both NHW (AUC: 18,965±648 vs. 15,797±371, p=0.0004) and AA (AUC: 18,965±648 vs. 15,801±497, p=0.0005) PCOS women without OSA. Glucose responses did not differ significantly between AA PCOS women with OSA and AA PCOS women without OSA (AUC: 17,104±965 vs. 15,801±497, p=0.15). Similarly, ISR was higher in NHW PCOS women with OSA compared to both NHW (AUC: 5,648±488

vs. 3,907±231, p=0.0006) and AA (AUC: 5,648±488 vs. 3,981±235, p=0.0011) PCOS women without OSA. ISR did not differ significantly between AA PCOS women with OSA and AA PCOS women without OSA (AUC: 4,827±461 vs. 3,981±235, p=0.09). CONCLUSIONS: OSA has a greater impact on glucose and ISR during an oral glucose challenge in NHW compared to AA women with PCOS. Future studies would benefit from including race when evaluating metabolic outcomes in women with PCOS. **References**: [1]Fogel et al., J Clin Endocrinol Metab. 2001: 86:1175–1180. [2]Kapsimalis et al., Sleep. 2002; 25:499–506. [3]Kapsimalis et al., Sleep. 2002; 25:412–419. [4]Polonsky et al., J Clin Invest. 1986 Jan; 77(1):98–105.

Thyroid

THYROID DISORDERS CASE REPORTS II

Delayed Hypersensitivity to Levothyroxine, and Oral Desensitization

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DELAYED HYPERSENSITIVITY TO LEVOTHYROXINE, AND ORAL DESENSITIZATION

Introduction- Hypothyroidism is a common endocrine disorder, affecting about 4.6 percent of the U.S. population aged 12 and older. The most common treatment is synthetic thyroxine hormone supplementation-levothyroxine, starting at 1.6 mcg/kg.Hypersensitivity reactions to levothyroxine are rare. Two cases have been published of successful oral desensitization, for suspected IgE mediated reactions. There are no published protocols describing induction of drug tolerance to immunologic, non-IgE mediated reaction to levothyroxine. The objective of this case report is to describe a novel outpatient protocol, for oral desensitization to levothyroxine, in the setting of a delayed immunologic (non-IgE mediated) reaction.

Case report- A 66 year old male with history of hypothyroidism, diagnosed in 2010 presented to outpatient endocrinology. Between 2010 and 2019, the patient was on multiple brands and formulations of levothyroxine. He noticed an itchy, raised rash on abdomen, chest and arms, within a few months after starting each of the above. No mucosal involvement or signs of end organ damage were noted. The rash was deemed a type IV delayed hypersensitivity reaction, based on history and histological findings on biopsy. The patient reported clearance of the rash when he was off any form of thyroid supplementation, and reappearance of the rash when he re-trialed it. The patient had normal thyroid stimulating hormone (TSH) levels while he was on supplementation despite the rash. The patient's TSH after discontinuing treatment was 104 (uIU/mL) and free thyroxine (T4) was 0.13 ng/dl (0.9–1.7). All components of previous brands of levothyroxine were compared and no common ingredient was thought to be contributing to hypersensitivity reactions. Subsequently, an oral desensitization protocol was initiated at 0.075 mcg daily with weekly increase in doses over seven weeks to reach a target dose of 75 mcg.

Discussion- The patient was tried on different brands of levothyroxine and dessicated thyroid hormone. He consistently developed a type IV hypersensitivity reaction within a few months after starting them. The patient had uncontrolled TSH levels after discontinuing the treatment and was at risk of complications of untreated hypothyroidism. This necessitated the need for desensitization. There have been previous case reports of oral or IV desensitization, in suspected IgE mediated reactions, but we describe the first case of induction of levothyroxine tolerance in an immunologic non-IgE mediated reaction. Subsequently, the patient tolerated a therapeutic dose of levothyroxine, with no appearance of rash or itching, for almost 6 months. This case report describes a novel approach to levothyroxine desensitization over a period of seven weeks in an outpatient setting in response to a delayed type hypersensitivity reaction.

Neuroendocrinology and Pituitary

RESEARCH ADVANCES IN PITUITARY TUMORS

Tissue-Specific Tumorigenesis in Multiple Endocrine Neoplasia Type I

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Tissue-Specific Tumorigenesis in Multiple Endocrine Neoplasia Type I

While a germline heterozygous mutation in the Multiple Endocrine Neoplasia type 1 (MEN1) gene predisposes tumor formation in specific tissues such as the endocrine pancreas, parathyroid glands and anterior pituitary, this tissue-specific tumorigenesis is not dependent on *MEN1* mutations alone. In fact, a homozygous deletion of *Men1* in mouse pancreatic exocrine tissue does not result in tumor formation, suggesting a tissue-specific mechanism. Loss of menin activates a menin-interacting protein retinoblastoma-binding-protein 5 (RBBP5). Since RBBP5 transcriptionally regulates DNA methyltransferase 1 (*DNMT1*), this causes global DNA hypermethylation and subsequent tumorigenesis in MEN1-target endocrine tissues. We hypothesize that while RBBP5 is ubiquitously expressed, it exclusively binds to the *DNMT1* promoter in MEN1-target-tissues through its recruitment by tissue-specific factors. Using chromatin immunoprecipitation, we demonstrated that Rbbp5 is bound to the *Dnmt1* promoter in MEN1-target-tissues, while not in non-target tissues. Following a high-throughput genome-wide approach, we identified two candidate factors that may recruit Rbbp5 to the *Dnmt1* promoter. Immunohistochemistry showed MEN1-target-tissue-specific expression of these target factors. Co-immunoprecipitation revealed MEN1-target-tissue-specific binding of Rbbp5 to the factors. In conclusion, Rbbp5 binds the *Dnmt1* promoter in MEN1-target-tissues and we have identified candidates for Rbbp5 recruitment to the *Dnmt1* promoter that must be tested further to determine their role in the observed tissue specificity of MEN1-related tumorigenesis.