an increased risk for heart disease. Using a mouse model of mental stress induced by restraint, we mimic the biochemical and physiologic changes observed in chronically stressed humans, which is characterized by an increase in circulating glucocorticoids, such as cortisol. Middle-aged mice (6 months old) as well as old-aged mice (18 months old) were used to differentiate the effects of aging on the burden of mental stress associated cardiovascular disease. Genes implicated in cardiomyopathy and CVD were found to be significantly up-regulated, not only immediately after a two-week stress period, but remained significantly up-regulated after the mice were allowed to recover stress-free for 5 weeks. Gene expression of the glucocorticoid receptor was down-regulated following exposure to chronic stress, suggesting an involvement of the hypothalamic-pituitary axis negative feedback loop. Gene expression of markers for hypertrophy (MHY7, ACTA1, NPPB) were upregulated and persisted in upregulation after mice were allowed to recover. Hypertrophy was further indicated by heart weight to tibia length ratios. Significant changes in aortic samples also implicate an involvement of the vasculature. Chronic stress in humans and mice leads to an increase in inflammatory and pro-coagulant markers. In our study, inflammatory markers (LCN, IL-6, IL-17c, PTGS2) were shown to be significantly increased immediately after the period of chronic stress, however the markers return to non-significant levels when mice were allowed a recovery period. Chronic mental stress has a lasting and direct deleterious effect on the cardiovascular system and it is essential to understand these implications in an aging population.

Thyroid
THYROID NEOPLASIA AND CANCER

In Silico Analysis of Polymorphism rs2228638 in Neuropillin-1 Demonstrated That This Variant May Hinder EBV Entry into Epithelial Cells.

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MON-522

The Epstein-Barr virus (EBV) is the first herpesvirus identified to be associated with human cancers and our group has demonstrated its association to thyroid cancer. It infects the vast majority of the world population causing latent and persistent infection, interfering in the metabolism of the host cells and triggering tumorigenic processes. Neuropillin-1 (NRP-1) is a type I transmembrane glycoprotein distributed on the cell surface of the virus, and considered vital for tumorigenesis. It has been demonstrated that EBV infection was increased by NRP1 expression. However, a conformational alteration of NRP1 could interfere with virus internalization into epithelial cells. The rs2228638 polymorphism of NRP1 may modify the molecule tridimensional configuration. In order to better understand the role of this polymorphism, based on NCBI dbSNP and UniProt databases, we evaluated the effect of the amino acid change in the protein structure using bioinformatics tools including SIFT, Align GVGD, PolyPhen-2, SNAP, PANTHER, PredictSNP, nsSNPAnalyzer, PROVEAN, SNP&GO, PMut and MuPRO. PANTHER prediction indicated that the polymorphic variant could produce a change in function. MuPRO indicated that the amino acid exchange produced by the polymorphism decreases protein stability. However, none of these tools showed conformational alteration. In conclusion, the presence of the rs2228638 polymorphism of NRP-1 may cause functional but not morphological changes that hinder EBV entry into the epithelial cells.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY CASE REPORTS I

Gigantism and Hypothalamic Obesity: Rare Endocrine Manifestations of Neurofibromatosis Type 1

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SAT-054

Background: Neurofibromatosis type 1 (NF-1) is a heritable, autosomal dominant, multisystem disorder caused by mutations or deletions in NFI, with approximately 30-50% of cases arising from de novo mutations. In the pediatric population, growth hormone deficiency is among one of the most commonly described endocrine sequelae, although aberrations of pubertal development are also commonly seen.

Clinical Case: A 3-year-old female, who was clinically diagnosed with NF-1 at the age of 4 months based on the presence of multiple café-au-lait macules, underwent screening MRI, which noted a left optic glioma and a hypothalamic mass favored to represent a hypothalamic glioma. Review of her growth chart showed a height much greater than the 99th percentile, with an increase in height velocity beginning 1 year prior. Weight was also noted to be much greater than the 99th percentile, with an increase in weight gain coinciding with the timing of alterations in linear growth. Mid-parental height is at the 95th percentile, and the patient’s height had tracked between the 86th and the 99th percentiles until age 2 years. Weight had tracked between the 68th and the 95th percentiles during that period. Initial laboratory evaluation showed an IGF-1 of 644 ng/mL (26-164 ng/mL). Gonadotropins were prepubertal; prolactin and thyroid studies were normal. ACTH stimulation demonstrated a rise in serum cortisol from 6.8 mcg/dL to 30.2 mcg/dL at 60 minutes. Growth hormone failed to suppress following an oral glucose load with a baseline GH of 4.4 ng/mL and values of 3.7, 6.5, 6.8, and 9.0 ng/mL at time +30, +60, +90, and +120 minutes respectively. Leuprolide stimulation did not
show significant rises in gonadotropins. Bone age was advanced by more than 1 year. The patient was started on subcutaneous octreotide with a decrease in IGFB-1 to 258 ng/mL after 1 month of therapy. On treatment, linear growth velocity slowed with no interval height gain over the initial 1-month period; however, the patient’s weight continued to increase with a gain of 1.8 kg. Parents additionally reported hyperphagia, which prompted concern for hypothalamic obesity in the setting of her known hypothalamic mass. Thyroid function remained normal on somatostatin therapy. To date, there has been no concern for diabetes.

**Conclusion:** Growth hormone excess may rarely complicate a diagnosis of NF-1 in the setting of intracranial gliomas. Increased height velocity and/or tall stature for family should raise clinical suspicion and prompt evaluation. Hyperphagia and significant increases in weight in the setting of hypothalamic gliomas in patients with NF-1 should raise suspicion for hypothalamic obesity and prompt lifestyle modifications to curb ongoing weight gain.

**Bone and Mineral Metabolism**

**NEW INSIGHTS INTO PTH AND CALCIUM RECEPTOR SIGNALING**

**Identification of the First Case of Acquired Autoimmune Parathyroid Hormone (PTH) Resistance Due to PTH1 Receptor (PTH1R) Autoantibodies**

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**OR07-01**

**Background:** Here we describe a patient who presented with symptomatic hypocalcemia and a biochemical picture suggestive of PTH resistance. PTH resistance is a hallmark of pseudohypoparathyroidism, a heterogeneous group of rare disorders caused by genetic or epigenetic alterations of PTH/PTHrP signaling. However, PTH receptor-related autoimmune etiology has not been identified as the underlying mechanism for PTH resistance. Here we describe the first case of acquired autoimmune PTH resistance that is secondary to PTH1R autoantibodies.

**Clinical Case:** A 12 yo male with left hip pain underwent a closed reduction for left slipped capital femoral epiphysis. The pre-op evaluation revealed hypocalcemia (serum Ca 7.7 mg/dL; nL: 8.8-10.2), creatinine 0.46 mg/dL (0.5-1.0), TSH 3.16 uU/mL (0.3-4.2), FT4 1.36 ng/dL (0.8-1.8). Oral calcium and vitamin D supplementation was begun, and 2 wks later, follow-up evaluation revealed serum Ca of 9.4 mg/dL, intact PTH 4.6 pg/mL (10-69), phosphorus 5.9 mg/dL (3.5-5.3), 25-OHD 26 ng/mL (30-100), and a normal chromosomal microarray. Bone density (DXA) Z-scores for hip and spine were -1.7 and 0.8, respectively. At age 13 he underwent bilateral osteotomy due to bilateral hip dysplasia and removal of hardware the next year. At age 15 he underwent left total hip replacement for avascular necrosis. In the post-operative period hypocalcemia recurred (5.9-6.7 mg/dL), and he was referred for endocrine evaluation. He was of mixed African American treatment with Calcitriol and Calcium supplements was initiated with good clinical response. Within 10 years of follow-up, the patient developed autoimmune hypothyroidism, alopecia and an unusual form of membranous glomerulonephritis, raising the suspicion for an autoimmune etiology for PTH resistance. Luciferase immunoprecipitation system assay identified antibodies against PTH1R with mapping to the N-terminal extracellular ligand-binding domain (amino acids 1-178). Using an in vitro biological assay in GP-2.3 cells, we found that the antibodies derived from the patient’s serum blocked PTH downstream signaling via G alpha/cAMP/protein kinase A pathway in a concentration-dependent manner.

The patient’s autoantibody profile led to the diagnosis of additional autoimmune diseases, including atrophic gastritis and Sjogren syndrome. Lymphocyte immunophenotyping using flow cytometry revealed an overall normal B and T cell profile, but with decreased frequencies and numbers of switched and non-switched memory B cell subsets and an increased frequency and number of the CD5+ naïve cell population. Genes associated with autoimmune inflammatory disorders were sequenced but no pathologic changes were detected.

**Conclusions:** Identification of the first case of autoimmune PTH resistance secondary to PTH1R autoantibodies extends the etiologic spectrum of hypoparathyroidism and should be considered when a patient presents with findings consistent with pseudohypoparathyroidism, especially in the presence of additional autoimmune diseases.

**Pediatric Endocrinology**

**PEDIATRIC ENDOCRINE CASE REPORTS I**

**A Novel De Novo GATA3 Gene Mutation in an Adolescent with HDR Syndrome**

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**SAT-065**

**Background:** GATA3 encodes a transcription factor critical for embryonic development of the parathyroid glands, kidney, inner ear, thymus, and the central nervous system. Heterozygous loss-of-function mutations in GATA3 are associated with hypoparathyroidism, sensorineural deafness and renal disease (HDR syndrome). **Clinical Case:** A 12 yo male with left hip pain underwent a closed reduction for left slipped capital femoral epiphysis. The pre-op evaluation revealed hypocalcemia (serum Ca 7.7 mg/dL; nL: 8.8-10.2), creatinine 0.46 mg/dL (0.5-1.0), TSH 3.16 uU/mL (0.3-4.2), FT4 1.36 ng/dL (0.8-1.8). Oral calcium and vitamin D supplementation was begun, and 2 wks later, follow-up evaluation revealed serum Ca of 9.4 mg/dL, intact PTH 4.6 pg/mL (10-69), phosphorus 5.9 mg/dL (3.5-5.3), 25-OHD 26 ng/mL (30-100), and a normal chromosomal microarray. Bone density (DXA) Z-scores for hip and spine were -1.7 and 0.8, respectively. At age 13 he underwent bilateral osteotomy due to bilateral hip dysplasia and removal of hardware the next year. At age 15 he underwent left total hip replacement for avascular necrosis. In the post-operative period hypocalcemia recurred (5.9-6.7 mg/dL), and he was referred for endocrine evaluation. He was of mixed African American