

Reproductive Endocrinology

MALE REPRODUCTIVE CASE REPORTS

Concomitant Mutations in the POR and AR Genes in a Boy Presenting with Micropenis and Premature Adrenarche

Eleni Dermitzaki, MD¹, Emmanouil Manolakos, PhD², Kleonthis Kleonthis, MD³, George Mastorakos, MD⁴, Dimitrios T. Papadimitriou, MD, MSc(2), PhD³.

¹Pediatric Endocrine Clinic, Athens, Greece, ²Access to Genome, Athens, Greece, ³Pediatric Endocrine Clinics, Athens, Greece, ⁴Areteio Hospital, Athens, Greece.

SUN-028

Concomitant mutations in the POR and AR genes in a boy presenting with micropenis and premature adrenarche

Background: Micropenis is caused either by a defect in androgen synthesis, conversion to Dihydrotestosterone, or action due to mutant androgen receptor. Premature adrenarche is caused by excess of adrenal androgens.

Clinical case: A 6,5-year-old boy presented to our pediatric endocrinology clinic due to increased body weight and hyperthyretropinemia. Physical examination revealed premature adrenarche with testicular volume 1,5 ml, micropenis (4cm, <-2 SDS) and acanthosis nigricans. His linear growth presented an acceleration the last 2 years from +0.85 to +1.81 SD and his bone age was advanced by 2 years with a statural height at -0.5 SD, not in accordance with the mean parental height (+0.90 SD). At the same time, his BMI was increased from +1,36 to +3,64 SDS.

Laboratory investigations for premature adrenarche with synacthen test revealed mild elevation of compound-S 15,4 ng/dl at 60', which could be theoretically attributed to partial 11- β -hydroxylase deficiency (CYP11B1). DHEA was also elevated 2,1 ng/ml with an increased DHEA/ Δ 4 ratio at 20 (normal < 10) which could be explained in the case of partial 3- β -Hydroxysteroid dehydrogenase deficiency.

Method: Whole exome sequencing was performed targeted to a gene panel related to premature adrenarche.

Results: A heterozygous mutation c.[1174C>T]+[1174C>T]; p.[Pro329Ser]+[Pro329Ser] in exon 1 in Androgen Receptor (AR) gene (X-linked) was found to the patient and his mother. The mutation, according to Human Gene Mutation Database, can cause disorder of sex development (DSD), partial androgen insensitivity syndrome (PAIS), infertility and hypospadias. Additionally, sequencing of the coding region of the P450 oxyreductase (POR) gene revealed a heterozygous mutation c.[642-5C>G] in exon 7, which in homozygosity can cause steroidogenesis disorder due to oxyreductase deficiency. This heterozygous POR mutation was found to the patient and his father.

Discussion: Our patient carries mutations in the AR and in POR genes. The AR mutation is obviously responsible for micropenis in our patient. CYP11B1 and 3 β -Hydroxysteroid dehydrogenase genes were normal. POR deficiency is a disorder of steroidogenesis with phenotypic spectrum ranging from PCOS to ambiguous genitalia and glycocorticosteroid deficiency or even to classic Antley-Bixler syndrome (1).

Conclusion: The genetic and hormonal results in our case imply a role for POR in the CYP11B1 gene expression, which is reported for the first time to our knowledge.

1.

Concomitant Mutations in the P450 Oxidoreductase and Androgen Receptor Genes Presenting with 46,XY Disordered Sex Development and Androgenization at Adrenarche. *J Clin Endocrinol Metab.* 2010 Jul; 95(7): 3418-3427

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

Secondary Hyperparathyroidism and Other Complications in a Post-Roux-En-Y Patient: A Case Report

Jessica Michelle Chan, B.A., Bradley S. Havins, M.D. Touro University Nevada, Henderson, NV, USA.

MON-346

Roux-en-y Gastric Bypass is a very common surgical procedure in managing morbid obesity. Approximately 303,890 roux-en-y surgeries were performed in the United States in between the years of 2012 to 2017, and the number is steadily increasing as more Americans are diagnosed with obesity.¹

This featured case report describes a 52-year-old female presenting with complications seven years following Roux-en-y gastric bypass. Four years post-operatively, she presented to the ER with a pelvis fracture. It was incidentally found that she had osteoporosis with a t-score of -2.9. It was also found that her bone mineral density (BMD) for women for her age was low with a z-score of -3.5 and her 10-year probability of getting fractures was high with a Fracture Risk Assessment Tool (FRAX) score of 6.2%. Seven years following Roux-en-y gastric bypass, she presented to our primary care office with Vitamin B12 deficiency and secondary hyperparathyroidism due to Vitamin D deficiency. We attempted to correct the deficiencies with high dose of Vitamin D, Vitamin B12, and calcium citrate. Eight months later, the B12 levels were normalized, but the secondary hyperparathyroidism and Vitamin D deficiency were not corrected. This case illustrates the complications that can occur following a Roux-en-y Gastric Bypass, importance of supplement compliance, and proper follow-up with Roux-en-y patients.

Abstract keywords: Post-roux-en-y, secondary hyperparathyroidism, bypass surgery, complications

Endnotes

¹ American Society for Metabolic and Bariatric Surgery. (2018). *Estimate of Bariatric Surgery Numbers, 2011-2017* | American Society for Metabolic and Bariatric Surgery. [online] Available at: <https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers> [Accessed 31 Oct. 2019].

Diabetes Mellitus and Glucose Metabolism

DIABETES DIAGNOSIS, TREATMENT AND COMPLICATIONS

A Test for Variation in Insulin Concentrations at the Wilford Hall Ambulatory and Surgical Center

Craig Jenkins, DO¹, Dennis P. Lovett, PhD², Joseph Brinkman, PhD¹, Joshua Tate, MD¹, Thomas Gibbons, PhD¹, Derrick Beckman, MD¹, Lydia Jenkins, DO¹, Jana Wardian, PhD³.

¹US Air Force, San Antonio, TX, USA, ²Wilford Hall Ambulatory

Service Center, San Antonio, TX, USA, ³Diabetes Center of Excellence, San Antonio, TX, USA.

SUN-627

Background

Wilford Hall Ambulatory and Surgical Center is the Department of Defense's largest outpatient ambulatory surgical center serving over 55,000 patients, and is the U.S. Air Force's flagship medical facility for outpatient care.

As with the measurement of any medication concentration or lab value, there is some reasonable expectation that there may be some variability between the reported value and the objective measurement. However, expectations are that variability should be minimal in order to ensure reliable doses of medication. In the case of diabetes management, insulin concentration variability should be kept to a minimum for both its life-saving and stress-mitigating effects. Insulin in the correct doses is lifesaving for type 1 Diabetes, so understandably, the impact of degraded insulin is catastrophic. In both type I and type II diabetes, "diabetes distress" can lead to poor self management and is linked to higher A1C levels. A study published in 2017 testing insulin after receipt from their cold supply chain found shockingly low concentrations of insulin. Recent literature published in the Journal of Diabetes Science and Technology reported that insulin concentrations in randomly tested vials not only failed to meet a pre-established concentration standard per unit of insulin, but also had concerning variability. The prevalence of Diabetes in the Department of Defense population is approaching 20%, making the impact of degraded insulin concerning. There are expectations of variability in any medications prescribed, but the FDA states that the expected insulin concentration should be 95% or greater.

Methods

Overall, 40 vials representing two different types of insulin (20 vials of Novolog and 20 vials of Lantus) were collecting from the military pharmacy and transported to the clinical research laboratory for analysis. Following baseline analysis, half of the vials were stored in refrigerated conditions of 2-8 degrees Celsius; the other half were stored at room temperature according to manufacturer's directions.

Results

At the laboratory, all vials underwent initial analysis to determine concentration at baseline. The Novolog insulin was found to have a concentration range of 105.1% to 107.7% and the Lantus insulin concentration was 99.0% to 103.9%. Thus, all vials met the minimum concentration of 95 U/ml at time of baseline testing. Vials will be tested weekly to determine if degradation occurs under refrigeration and at room temperature.

Discussion

Given the high cost of insulin and the high impact on the health of the person with diabetes, assurance of a minimum of 95 U/ml must be met. If this is not met, investigation of the cold supply chain should identify the source of the problem and address it. Our study demonstrates that Novolog and Lantus were meeting the minimum concentration upon receipt at the pharmacy.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Deletion of Hepatic Kisspeptin Results in Abnormal Glucose Metabolism in Female Mice

Bahaa Alogaily, Ph.D., Hyokjoon Kwon, Ph.D., Ariel L. Negron, PhD, Fredric E. Wondisford, MD, Sally Radovick, MD.

Robert Wood Johnson Medical School/ Rutgers University, New Brunswick, NJ, USA.

SUN-261

Kisspeptin is a hypothalamic protein critical for neuroendocrine control of pubertal development and fertility and is modulated by nutritional signals. Kisspeptin has been localized to specific neurons located in the arcuate and anteroventral periventricular (AVPV) nuclei of the hypothalamus and is secreted to control GnRH mediated pubertal maturation and reproduction. Kisspeptin has also been localized to peripheral tissues including the liver, fat, gonads, intestine and placenta, although its role in these tissues is unclear. The objective of current study is to define the role of hepatic kisspeptin as a metabolic sensor. A floxed *Kiss1* mouse has been developed, and ablation of liver-specific *Kiss1* was achieved in two to three month old *Kiss1^{fl/fl}* male and female mice given a single tail vein injection of thyroid hormone-binding globulin (TBG) promoter-driven Cre recombinase adeno-associated virus (AAV-CRE). A control group of *Kiss1^{fl/fl}* male and female mice received an injection of AAV-GFP, expressing green fluorescent protein. Two weeks after injection, a glucose tolerance test (GTT) was performed followed by an insulin tolerance test. To determine whether changes had occurred in the reproductive axis, estrous cyclicity was assessed by daily vaginal smears and estrous cycle phases determined by vaginal cytology. Mice were euthanized four weeks post-injection and tissues were collected for RNA extraction and gene expression analysis via qRT-PCR. As expected, qRT-PCR data showed absence of *Kiss1* expression in the liver of AAV-CRE mice compared to AAV-GFP mice with no changes in kisspeptin gene expression were noted in the ovary, testes, spleen, pancreas, arcuate or AVPV. Estrous cyclicity was also not affected by viral ablation of hepatic *Kiss1*. Elevated fasting glucose and glucose intolerance in the GTT were found in AAV-CRE compared to AAV-GFP females ($P < 0.05$). No differences in AAV-CRE and AAV-GFP male mice were found, indicating the importance of *Kiss1* in glucose homeostasis in females. The insulin tolerance test was not statistically different between groups or treatments. Further research is required to elucidate the mechanism by which hepatic kisspeptin alters glucose metabolism in mice in a sexually-dimorphic fashion.

Diabetes Mellitus and Glucose Metabolism

GESTATIONAL DIABETES, DIABETES IN PREGNANCY, AND IN UTERO EXPOSURES

Sex-Specific Difference in REG3G Expression Directs the Maintenance of Islet Function in Offspring of Obese Mice

Jose Casanovas, PhD¹, James C. Jarrell, BSc², Kok Lim Kua, MD¹.

¹Indiana University School of Medicine, Indianapolis, IN,