Reproductive Endocrinology

SEX, GENDER, AND HORMONES

11-Oxygenated C19 Steroids Are Alternative Markers of Androgen Excess in Children with Premature Adrenarche and Premature Pubarche

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Premature adrenarche (PA), the early onset of pubic hair and/or axillary hair/odor in children, is associated with elevated adrenal androgens and precursors in the absence of gonadotropin-dependent puberty. Laboratory data in PA classically demonstrate increased DHEAS, T, and A4 levels that correlate with pubic hair development. In premature pubarche (PP), the clinical presentation occurs in the absence of elevated DHEAS, T, and A4. PA is associated with insulin resistance and progression to metabolic syndrome (MetS) and PCOS; it is unclear which of these children are at risk for metabolic abnormalities.

Adrenally-derived 11-oxygenated C19 steroids (11oAs) have comparable androgenic potency to T and DHT and are elevated in disorders of androgen excess. We sought to characterize the 11oA profiles of children with PA/PP and controls and to correlate them with traditional androgens and metabolic markers, including criteria for childhood MetS. A prospective cross-sectional study was performed of subjects with PA or PP (5 M, 14 F) and controls (2 M, 6 F) ages 3 – 8 yrs (F) or 3 – 9 yrs (M). Children with precocious puberty, steroid use, or recent illness were excluded. Fasting early morning serum was collected, a complete physical exam was performed, and BP and waist circumference were measured; a bone age was obtained only in PA/PP subjects. 11oAs (11OHT, 11KT, 11OHA4, 11KA4) were analyzed by LC-MS. Subjects were divided into PA (DHEAS ≥ 50 μg/dL, n=10) or PP (DHEAS < 50 μg/dL, n=9) for sub-analysis.

There were no significant differences in sex, race/ethnicity, BMI z-score, preterm gestation, birth weight, family history, or clinical criteria for childhood MetS. T, A4, DHT, DHEAS, and all 11oAs were significantly higher in PA/PP subjects. While lipids did not differ, insulin and HOMA-IR were higher in PA/PP vs. controls {insulin Mdn = 8.2 (IQR 3.5 – 10.0) vs. 2.0 (2.0 – 3.3) μIU/mL, $p < 0.03$; HOMA-IR Mdn = 1.8 (IQR 0.8 – 2.1) vs. 0.4 (0.4 – 0.8), $p < 0.03$}. In a sub-analysis of PA vs. PP, there were no differences in baseline characteristics or metabolic markers. DHEAS was elevated in PA vs. PP {Mdn = 95 (IQR 73 – 111) vs. 42 (36 – 46) μg/dL, $p < 0.00003$}, although no differences were noted in 11oA levels. Correlations of androgens and their precursors suggested best correlation of 11KT and 11OHA4 with T (ρ=0.87; ρ=0.87) and A4 (ρ=0.87; ρ=0.88). There was moderate correlation of 11KT and 11OHT with insulin (ρ=0.47; ρ=0.51) and HOMA-IR (ρ=0.43; ρ=0.47).

We conclude that PA and PP differ only by DHEAS (by definition) and not by insulin sensitivity or 11oA, consistent with 11oA – rather than DHEAS – mediating the phenotypic changes of pubarche. These pilot data are the first to report the early morning steroid metabolite levels including 11oAs in a phenotypically and metabolically well-defined group of PA, PP, and age-matched male and female controls. The relationships between PA, PP, risk for MetS, and 11oA warrant further study.

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS II

P-450 Oxidoreductase Deficiency with Antley Bixler Phenotype: A Novel Mutation

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P-450 Oxidoreductase Deficiency with Antley Bixler Phenotype: A novel mutation

ABSTRACT

Introduction

We present first case of 46 XY Disorder of Sex Development (DSD) from India due to P-450 Oxidoreductase Deficiency with Novel variant (p.Ala541Thr) in a heterozygous state.

Case Discussion

6 months old boy presented with ambiguous genitalia since birth. No history of neonatal crisis, failure to thrive and pigmentation of skin, maternal virilisation or drug ingestion during pregnancy. On examination: weight 6.2 Kg (3^{rd} centile), height 64 cm (3^{rd} centile), MPH-170 (25-50^{th} centile), head circumference 38 cm (−2.7 SD), vitals stable, trigonocephaly with fused anterior and posterior fontanelle, prominent pointed forehead, midfacial hypoplasia, up slanting eyes, hypertelorism and low set ears were present. Genitalia: 1.5 cm phallus like structure with foreskin, chordee, single perineal opening in form of peno-scrotal hypospadias, bifid scrotum with poor rugosity and poor pigmentation and both gonads (1 ml) were palpable in labio-scrotal fold with external masculinization score (EMS), 6/12 and Prader stage 4.

Investigations showed normal electrolytes and blood sugar, High basal ACTH, post stimulation cortisol 14mcg/dl, Basal 17-OHP was 8.6 ng/ml and post stimulation 12ng/ml, with low DHEAS 36.4 mcg/dl and androstenedione 0.42 ng/ml, LH 16.09 mIU/ml (elevated), FSH 2.97 mIU/ml (normal) and low Testosterone for his age. T/DHT 9.6 (normal<10) and Testosterone /Androstenedione ratio 0.95 (normal >0.8). Abdominal and Pelvic imaging showed normal adrenal glands and absent female internal genitalia, bilateral testis in labio-scrotal fold (right testis-6x6.5x11 mm, left testis-6.6x7x10 mm), corpora cavernosa and bifid scrotum. NCCT Head showed metopic craniosynostosis with trigonocephaly and hypotelorism. Skeletal survey showed bowing of femora. 20 cell Karyotype of peripheral blood lymphocyte was 46 XY. NGS was done of the POR gene, which revealed a heterozygous missense variation in exon 13 of the *POR* gene variant (p.Ala541Thr) which has not been reported yet.

The patient was initiated hydrocortisone, fludrocortisone, DHT gel and corrective surgery is planned.

Clinical learning

Although in PORD classically the inheritance is generally autosomal recessive, but manifesting heterozygotes are not uncommon[1]. This case also shows the value of Next gen sequencing and the role it can play in DSD

1. Scott RR, Gomes LG, Huang N, Van Vliet G, Miller WL. Apparent manifesting heterozygosity in P450 oxidoreductase deficiency and its effect on coexisting 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2007;92:2318–2322

Cardiovascular Endocrinology

PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

Role of Linagliptin on CD34+ Endothelial Progenitor Cells and Arterial Stiffness in Renal Function Impaired Type 2 Diabetes Subjects

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SUN-578

Title: Role of Linagliptin on CD34+ Endothelial Progenitor Cells and Arterial Stiffness in renal function impaired Type 2 Diabetes subjects.

Introduction: Endothelial Progenitor cells (EPCs) has been shown to be dysfunctional in both Type 2 Diabetes and Chronic Kidney Disease (CKD) leading to poor regeneration of endothelium and renal tubules. EPCs have been shown to be a robust cardiovascular disease (CVD) risk indicator. DPP4 inhibitor increase endogenous SDF1a which has been shown to increase CD34+ cells migration and thereby improve CVD risk. However, cellular mechanisms of DPP4i mediated improvement of CVD in patients with Type 2 Diabetes with established CKD is not established. **Hypothesis**: Linagliptin, a DPP4 inhibitor when added to insulin, metformin or both may recover endothelial function in a diabetic kidney disease (DKD) population. **Methods**: 31 subjects taking 1–2 grams of metformin and/or Insulin were enrolled in this 12 weeks, double blind, two-arm, randomized placebo matched trial, with 5 mg Linagliptin compared to placebo. Type 2 diabetes subjects (30–70 years old), HbA1c of 6.5–10%, and all stages of CKD were included. CD34+ cell number, migratory function, gene expression along with vascular parameters such as Arterial stiffness, biochemistry, resting energy expenditure and body composition were measured. Data were collected at week 0, 6 and 12. During trial HbA1C was maintained between 7–8% for all subjects. Every subject was used as their own control. A mixed model regression analysis was done with p value <0.05 considered significant. **Results**: A double positive CD34/CD184 cell count had a statistically significant increase ($p<0.02$) as determined by flow cytometry in treatment group though there was no statistically significant increase in CD34+ cell number, or colony formation units. Gene expression analysis on CD34+ cells showed reduced expression of TP53 ($p<0.04$). Arterial stiffness measures such as augmentation Index ($p<0.04$) along with augmentation pressure ($p<0.02$) were significantly reduced in the treatment group. A reduction in LDL: HDL ratio was noted in treatment group ($p<0.04$). No change in renal function was noted during the 12 week period.. We are currently analyzing urinary exosome based data to enquire further into renal function **Conclusions**: In DKD subjects, Linagliptin promotes an increase in CXCR4 expression on CD34+ progenitor cells with a concomitant improvement in arterial stiffness and LDL parameters within 12 weeks of intervention.

Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Antenatal Oral Iron Supplementation, FGF23 and Bone Metabolism in Kenyan Women and Their Offspring: A Randomised Controlled Trial

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SUN-359

Objectives: FGF23 decreases reabsorption and increases phosphate excretion in the kidney and regulates vitamin D metabolism. Maternal iron deficiency may be implicated in the pathogenesis of hypophosphataemia-driven rickets in offspring through perturbed FGF23 expression. We aimed to determine the effect of antenatal oral iron supplementation on maternal and neonatal markers of bone mineral regulation.

Methods: 470 rural Kenyan women with singleton pregnancies and haemoglobin concentrations ≥90g/L were randomly allocated to daily, supervised supplementation iron (60mg as ferrous fumarate) or placebo from 13–23 weeks gestational age until 1 month postpartum. We analysed maternal and neonatal plasma samples collected at birth, with primary outcomes being concentrations of FGF23 in its intact form (I-FGF23, the phosphate- and vitamin D-regulating hormone) and its C-terminal fragment (C-FGF23).

Results: In mothers and neonates, antenatal iron supplementation reduced C-FGF23 concentration by 62.6% (95%CI: -70.3% to -53.0%) and 15.2% (-28.4% to 0.3%), respectively; increased neonatal I-FGF23 concentration by 21.6% (1.2% to 46.1%); increased maternal hepcidin concentration by 136%, (86% to 200%); and decreased maternal 25-hydroxyvitamin D concentrations by 6.1nmol/L (1.2 to 11.0nmol/L). We found no effect on markers of bone turnover in either mothers or neonates. The magnitude of the