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