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Introduction: The genetic basis of human growth regulation has only been partly elucidated thus far. Therefore, finding causative genes in patients with short stature help in understanding precise pathophysiological mechanisms, establishing genotype-phenotype relationships and optimizing treatment. In order to extend our knowledge about the genes involved in short stature, we studied a unique cohort of consanguineous families with children with short stature from Sulaymani in Kurdistan, Iraq. **Patients and Methods:** Fifty-five consanguineous families, with children shorter than -2.3SDS at the time of examination (median height -3.3SDS, range -2.3 to -15SDS), who were examined at the endocrine outpatient clinic of the Department of Pediatrics, Sulaymani University College of Medicine between January 2018 and February 2020, were included in the study. In families with more than one child with short stature, the shorter sibling was selected as the proband (median age 8 years, range 1 - 15 years). Three probands were subsequently excluded due to the diagnosis of Turner's syndrome and Edward's syndrome**.** Consent was obtained from all families and probands' DNA was analyzed by Whole Exome Sequencing (WES) methods. The data were processed by a bioinformatic pipeline and detected variants were filtered using variant analysis software. Selected potentially pathogenic variants were confirmed using Sanger sequencing methods and evaluated by the American College of Medical Genetics (ACMG) standards and guidelines. **Results:** A monogenic cause of short stature, which explained the patient phenotype, was elucidated in 13 of 26 families who were analyzed thus far. Seven families had multiple affected children making a total of 22 patients with a positive genetic diagnosis. Pathogenic or likely pathogenic variants (according to the ACMG standards) were found in genes involved in the GH-IGF-1 axis (*GHR*), in the extracellular matrix of the growth plate (*COL1A2*, *MMP13, LTBP3,* and *ADAMTS17*), in the regulation of chondrocytes (*NPR2* and *CTSK*), transporter coding genes (*SLC34A3*), and other genes (*PTCH1, GALNS, DNACJ21, ZSWIM6, GNPTG*). Among them, there are 9 novel variants and 10 homozygous variants including variants in genes causing syndromic short stature. Unexpectedly, we successfully identified three cases of autosomal dominant short stature (variants in genes *NPR2, COL1A2, PTCH1)* as well. The remaining probands from 26 families are still being analyzed. **Conclusion:** With the help of NGS methods, we have successfully elucidated the genetic cause of short stature in nearly 50% of patients who were analyzed thus far. These results further strength the concept that genes affecting the growth plate (chondrocytes and the extracellular matrix) play a crucial role in growth regulation. **Acknowledgements:** The study was co-funded by grants AZV 18-07-00283 and GAUK 340420.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY: GROWTH AND DEVELOPMENT

Longitudinal Investigation of Pubertal Milestones and Hormones as a Function of Body Fat in Girls

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Background: Studies comparing the timing and pace of puberty in overweight/obese girls (OW/OB) vs normal weight girls (NW) have produced conflicting results; some suggest earlier activation of the central components of the reproductive axis in OB while others are more consistent with a peripheral source of estrogen (e.g. adipose tissue) driving puberty in OB. Importantly, there have been no longitudinal assessments of both clinical and biochemical pubertal markers in OB vs. NW. **Methods:** 90 healthy pre-menarchal girls (26 OW/OB, 54 NW) from the community, aged 8.2-14.7 years, completed 2.8 ± 1.7 (mean, SD) study visits over the course of 4 years. Visits included dual-energy x-ray absorptiometry to calculate percent total body fat (TBF), Tanner staging, breast ultrasound for morphological staging (BMORPH; stages A-E), pelvic ultrasound, hand x-ray (bone age, BA), blood tests for reproductive hormones, and urine collection to determine a vaginal maturation index (VMI), an index of estrogen exposure in urogenital epithelial cells. Menarchal status was determined at each visit and via follow-up questionnaires. The effect of TBF on hormones and markers of estrogen action, the pace of breast maturation, and age at menarche were determined using a mixed, multi-state, or Cox proportional hazards model, respectively. Mixed and Cox models controlled for BMORPH at visit 1 (V1) and race. **Results:** NW girls were older than OW/OB (11.3 vs. 10.2 yrs, $p<0.01$) at V1, more likely to be non-Hispanic White (66 vs. 40%, $p=0.03$), and had more advanced breast morphology BMORPH ($p<0.01$). LH, E2, VMI, BA, and ovarian and uterine volume increased with time with no effect of TBF. There was an interaction between time and TBF for FSH, INHB, E1, Total T, Free T, and A'dione ($p<0.05$): levels were initially similar in all TBF groups, but after 1 yr, levels increased in girls with higher TBF, plateaued in girls with mid-range TBF, and decreased in girls with lower TBF. Girls with higher TBF progressed through BMORPH stage D (corresponding to growth/arborization of the breast ductal system), more slowly than girls with lower TBF but achieved menarche at a younger age (risk 1.04x higher per 1 unit increase in TBF). **Conclusions:** Intensive reproductive phenotyping of girls during the pubertal transition reveals that both the neuroendocrine and ovarian components of the axis are generally preserved in girls with higher TBF but that the axis appears to be activated earlier than in girls with lower TBF. In late puberty, however, girls with higher TBF demonstrate subtle differences in standard hormonal (e.g. serum FSH, INHB,

and androgen) and clinical (e.g. delayed growth of breast bud) markers of puberty. Investigation of the mechanistic basis for these differences and their potential clinical consequences for girls with higher TBF deserves further study.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY: GROWTH AND DEVELOPMENT

Self-Reported Feelings of Adult Patients With Differences of Sex Development (DSD) Regarding Genital Surgical Procedures

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Introduction: Differences of sexual development (DSD) define congenital diseases in which there is an atypical development of chromosomal, gonadal or anatomical sex, and may present varying degrees to genital atypia. There has been a discussion about the ideal time for surgical approach of atypical genitalia. S, because some non-governmental entities argue that the surgical approach should be delayed until adulthood after the patient's consent. **Objective/methodology:** To analyze the perspectives of adult DSD patients followed at a reference center in São Paulo on the surgical approach to correct atypical genitalia, through a semi-directed interview. **Results:** Thirty-seven adult patients with atypical genitalia were interviewed. Patients' mean age was 36 years. 70% of them had atypical genitalia diagnosed at birth. The patients' median age at the genitoplasty approach was 5 years (1 to 35 years). The median time interval between the beginning of the follow-up at the referral center and the surgical procedure was 1.9 years. When asked about the ideal period/age for genitoplasty, 72.2% considered the childhood, 16.7% cited when they're teenagers, 8.3% in adulthood and 2.8% did n't know. The discomfort reported by the patients related to atypical genitalia decreased after the surgical approach: from 3.8 to 2.9 $p < 0.01$ (on a scale of 1 "without discomfort' to 4 "extreme discomfort"). Insecurity about the appearance of genitalia and functionality during sexual intercourse influences negatively affective relationships. Four (10.8%) patients presented gender dysphoria, all of them with 46,XY DSD, three with partial gonadal dysgenesis (all approached surgically before being admitted to our referral service) and one with 5-alpha-reductase 2 deficiency**. Conclusion:** Most 46,XY DSD patients considered childhood the ideal time to correct their atypical genitalia. An early follow-up in a reference center and an adequate evaluation by a multidisciplinary may influence the positive results associated to the surgical approach of the atypical genitalia in childhood and the low prevalence of gender dysphoria in adulthood.

Reproductive Endocrinology

ANDROGENS ACROSS SEX, GENDER AND THE LIFESPAN

Peripubertal Anti-Mullerian Hormone Levels Are Associated With Hyperandrogenemia During Adolescence: The Avon Longitudinal Study of Parents and Children

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Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women and is associated with negative reproductive and metabolic outcomes including subfertility, pregnancy complications, metabolic syndrome, and type 2 diabetes. The diagnosis of PCOS cannot be made until reproductive maturity, when the diagnostic criteria of hyperandrogenemia and oligomenorrhea develop. However, studies have described early metabolic and reproductive characteristics of the disorder in girls at increased risk, suggesting the pathogenesis starts much earlier. Indeed, studies in animal models suggest that exposure to excessive androgen or anti-Mullerian hormone (AMH) levels during critical developmental periods can program the offspring to develop the metabolic and reproductive features of PCOS during reproductive maturity.

We investigated early maternal or peripubertal factors associated with hyperandrogenemia during adolescence using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a United Kingdom birth cohort which has been ongoing since 1991. We performed linear regression to test for an association of testosterone levels at 15 years with peripubertal reproductive and metabolic phenotypes and with maternal measures of insulin sensitivity. Peripubertal phenotypes included AMH levels at 7, 9, and 11 years, and androstenedione, DHEAS, SHBG, IGF-1, fasting insulin, QUICKI, post-glucose insulin, leptin and adiponectin at age 8 years. Maternal phenotypes included fasting insulin levels and QUICKI at a post-partum visit. Unadjusted and adjusted analyses including the covariates pubertal stage, ethnicity, maternal and daughter BMI were performed.

Testosterone levels at age 15 years were significantly positively associated with AMH levels at ages 7(N=299), 9(N=295), and 11(N=300) years in both the adjusted and unadjusted models (Age 7 unadjusted $P<0.0001$, adjusted $P=0.01$; Age 9 unadjusted $P<0.0001$, adjusted $P=0.003$; Age 11 unadjusted $P<0.0001$, adjusted $P=0.02$). Testosterone at age 15 years was also associated with DHEAS at age 8 years using the unadjusted ($P<0.0001$) but not the adjusted model. There was no significant association between any of the other peripubertal metabolic and reproductive phenotypes or the maternal metabolic phenotypes of fasting insulin and QUICKI with testosterone level at age 15 years.

We have found a persistent and significant positive association of AMH levels at pre- or peri-pubertal ages with testosterone levels during adolescence, a developmental stage at which a clinical diagnosis of PCOS can be made. It