Methods: This study included girls (n = 349) of the Environment and Development of Children (EDC) cohort, a prospective cohort of healthy children started in 2012 with biennial visits to study the effects of environmental exposures on physical and neurobehavioral development. The BMI trajectories of girls with 3 or more measurements between 2 and 8 years of age (n = 242) were visually inspected to determine AR timing. After excluding preterm and multiple births, 204 girls were included and categorized according to the age at AR: group 1 (<3.9 years; n = 34, 17%), group 2 (3.9-5.9 years; n = 55, 27%) and group 3 (≥6 years; n = 115, 56%). AR groups were compared for differences in anthropometric measures, BA progression, and breast development. The relationships between AR and outcomes were analyzed with adjustment for age, gestational age, birthweight, physical activity and diet. **Results:** At age 2, there were no differences in anthropometric measures. By age 4, group 1 showed higher mean BMI z-scores (0.87) than groups 2 (-0.19) and 3 (-0.45) (P <0.001). The differences in BMI z-scores were significant between all 3 groups at 6 and 8-years (P <0.001, for all). Height differences became significant at 8-years (P = 0.010), with greater mean height z-score in group 1 (0.80) compared to group 3 (0.30). BA progression differed significantly between groups 1, 2 and 3 at 6-years (BA 6.87 vs. 6.44 vs. 6.36 years respectively; P < 0.001) and at 8-years (BA 9.65 vs. 8.82 vs. 8.60 respectively; P < 0.001). The inverse relationship between AR timing and BA remained significant after adjusting for covariates at 6 years (B = -0.222, P = 0.040) and 8 years (B = -0.468, P <0.001). Breast development occurred in 49 girls (24%) by age 8 with increased occurrence in the earlier AR groups: group 1 (n = 16, 47%), group 2 (n = 17, 31%), and group 3 (n = 16, 14%) (P for trend <0.001). When compared to group 3, the earlier AR groups had significantly increased risk of breast development at age 8 (OR 5.1, 95%CI 2.1-12.4 for group 1 and OR 2.4, 95%CI 1.1-5.4 for group 2, P <0.001 for both), after adjusting for covariates (P <0.05, for both). **Conclusions:** Girls who had earlier AR showed greater BA progression starting at 6 years and continuing at 8 years along with greater height at 8 years. These girls are at risk for early breast development after adjustment for covariates. AR timing may be a predictor for BA progression and onset of breast development in girls.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY: GROWTH AND DEVELOPMENT

Familial Short Stature - a Novel Phenotype of Growth Plate Collagenopathies

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Backround: Collagens are the most abundant proteins in the human body. In a growth plate, collagen types II, IX, X and XI are present. Defects in collagen genes cause heterogeneous syndromic disorders frequently associated with asymmetric short stature (e.g. Kniest dysplasia, spondyloepiphyseal dysplasia). Less is known about nonsyndromic collagenopathies - data about their frequency and subtle phenotypic signs are sparse, the information about their response to growth hormone (GH) treatment is lacking completely.

Aim: To evaluate the frequency of collagenopathies in familial short stature (FSS) children and to describe their phenotype, including growth hormone (GH) treatment response.

Methods: Out of 522 individuals treated in our center with GH from the indication of primary GH deficiency (GHD) or small for gestational age short stature (SGA-SS), 87 children with FSS fulfilled the inclusion criteria (pre-treatment height ≤-2 SD in both patient/their shorter parent, signed written informed consent) and were enrolled to the study. Next-generation sequencing was performed to search for variants in *COL2A1*, *COL9A1*, *COL9A2*, *COL9A3*, *COL10A1*, *COL11A1* and *COL11A2* genes. The results were evaluated using ACMG guidelines. The phenotype of children with (likely) pathogenic variants was described including the short-term GH treatment response (growth velocity and body-height SDS increase over three years of treatment). For statistical evaluation, parametric tests were used, p-values <0.05 were considered significant.

Results: A (likely) pathogenic variant in one of the collagen genes was found in 10/87 (11.5%) children. Their age was 12.5 years (median, range 6-17 years), their pre-treatment height was -3.1 SD (-2.4 to -4.3 SD). Their birth length (median -2.8 SD; range -0.7 to -4.1 SD) was more severely affected than birth weight (median -2.1 SD; range -1.0 to -2.7 SD). Eight children were treated with GH from SGA-SS indication, the remaining 2 were classified as mild GHD (maximal stimulated GH concentration 8.0 and 9.7 ug/l, normal brain MRI and examination of other pituitary hormones). Detailed anthropometric examination described mild asymmetry with shorter limbs and mild bone dysplasia signs (scoliosis, more pronounced lumbar lordosis, genua valga, limited elbow extension) in 2/10 and 4/10 affected children, respectively. Growth velocity improved from a median of 5.3 cm/year to 8.7 cm/year after one year of treatment (p<0.001, paired-sample T-test), height improved from a median of -3.1 SD to -2.2 SD after three years of therapy (p=0.001, ANOVA repeated measures analysis of variants).

Conclusion: Nonsyndromic collagenopathies are a frequent cause of FSS. The short-term response to GH treatment is promising.

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PEDIATRIC ENDOCRINOLOGY: GROWTH AND DEVELOPMENT

Growth Plate Genes Are Key Regulators of Growth: Lessons Learned From Children of Consanguineous Families From Kurdistan, Iraq

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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.

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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,