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

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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