genitalia development by W48. Tanner staging for pubic hair development remained stable for approximately 80% and decreased for 7% of children by W48. 52/53 treatment emergent adverse events were mild or moderate.
Conclusions: 6-month 45 mg subcutaneous leuprolide acetate is a promising treatment for CPP. It effectively suppressed LH, suppressed clinical signs of pubertal maturation and demonstrated a good safety profile. It also has the beneficial features of subcutaneous administration, small injection volumeand twice a year dosing. This may be a welcome addition to the armamentarium given the proposed shift in CPP therapies towards longer-acting formulations and subcutaneous injections.

Pediatric Endocrinology
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A Clinical Experience of Pubertal Induction in Female Patients With Congenital Hypogonadotropic Hypogonadism (CHH) From an Endo-ERN Referral Center

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Female congenital hypogonadotropic hypogonadism (CHH) is a rare condition, with a strong genetic background, characterized by absent or incomplete pubertal development, for which inductive treatment with sex-hormone is required. Although the available data, mostly coming from studies in patients with Turner syndrome, indicate transdermal estradiol (TDE) as the first-choice formulation, no internationally validated therapeutic schemes are currently available. Furthermore, data on CHH patients are certainly lacking and there is no standard of care for pubertal induction in this specific population. The aim of our work was the retrospective analysis of the data from a collection of case reports of pubertal induction in CHH patients referred to our Center. Six patients underwent induction with transdermal estradiol (TDE) at the starting dose of 0.1μg/kg/day (night-time for the first 4-6 months), increased every 4-6 months up to the adult dose, for a mean period of 2.86 ± 0.45 ys. Micronized progesterone (200 mcg) was introduced at reaching of 50μg dose or if breakthrough bleeding occurred. Treatment was monitored through clinical and anthropometric evaluations at each dose modification. The average age of induction was 17.25 ± 1.41 ys, with each bone age> 13 ys. Three out of six patients already had a Tanner B2 stage at diagnosis. The mean times of pubertal advancement were respectively 1.3 ± 0.46 ys for the achievement of B3, 2.13 ± 0.29 ys for the B4 and 2.35 ± 0.77 ys for menarche; all the patients reached an adult breast conformation (B5) in 2.81 ± 0.28 ys. These data are consistent with physiological pubertal progress. All of them achieved adequate uterine development (medium longitudinal diameter 72.2 ± 3.37mm), except one patient with suboptimal development (54mm). The final height (FH) was adequate in all patients, with SDS FH +1.6 (-0.43 - +3.38), in spite of an average growth of 4.11 cm (2.5-6) during the induction period and a growth rate > 2cm/year only in 50% of patients. No side effects were reported, and individual compliance and satisfaction were quite high. This clinical experience suggests that the adopted regimen, consistent with current literature, guarantees excellent efficacy and safety. However, further studies are needed to identify the optimal treatment in adolescents with CHH, taking into account their higher age at the start of induction, the modest impact on growth and final stature, to focus on the specific clinical objectives in these patients

Pediatric Endocrinology
DISORDERS OF PUBERTY

Defects in the GnRH Neuronal Migration factor, CCDC141, Lead to Self-Limited Delayed Puberty

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GnRH neuronal biology has been identified as a critical element in the pathogenesis of self-limited DP, previously implicated exclusively in the pathophysiology of idiopathic hypogonadotropic hypogonadism (IHH). We hypothesise that this condition may be inherited via genetic variants discoverable through whole-exome sequencing (WES), by focusing on genes involved in GnRH neuron development and function, and genes reported in IHH. We analysed WES data from large Finnish cohort with familial self-limited DP, focusing on genes recently reported in IHH. WES data of 100 DP families have been analysed with a total of 193 individuals: 100 probands, 158 affected and 35 unaffected family members. Potentially pathogenic rare variants segregating within cohort families were identified using a virtual panel of recently reported IHH genes (n=13). This analysis identified 6 rare potentially pathogenic variants in *CCDC141* in 25 individuals of 8 families which account for almost 10% of self-limited DP cases in this cohort, without variants identified in cohort control cases. Previous studies reported that homozygous or compound heterozygous mutations of *CCDC141* cause Kallmann syndrome and IHH, due to impaired GnRH neuronal migration. In this study, all 6 *CCDC141* variants were heterozygous missense variants predicted to be deleterious by *in silico* prediction tools. Most probands were male (n=7) with typical features of self-limited DP, with absence of secondary sexual characteristics, delayed bone age, and low gonadotropins and sex steroids at first presentation and spontaneous entry into puberty later than age of 14 years without treatment. The majority of pedigrees displayed good segregation of variants with the DP trait, following an autosomal dominant inheritance pattern. However, in two families, there was a complex inheritance pattern with compound heterozygosity (p.Ser55Cys and p.Asp767Asn) and possible incomplete penetrance. *In vitro*

study showed that the overexpression of four key *CCDC141* variants in HEK293 cells delayed cell migration, 72% in p.Ser55Cys (*p=0.04*), 66% in p.Gln507His (*p=0.04*), 65% in p.Asp767Asn (*p=0.02*), and 83% in p.Ala1073Thr (*p=0.01*), when compared to WT (100%). Moreover, WT-overexpressed cells increased the rate of cell migration when compared to non-transfected cells (100% vs 65%, *p=0.005*), reaffirming that *CCDC141* has a role in cell migration. In conclusion, heterozygous deficiency of CCDC141, previously reported to cause IHH, can cause self-limited DP due to abnormal GnRH migration during foetal development.

Pediatric Endocrinology
DISORDERS OF PUBERTY

Doppler Assessment of the Uterine Arteries for the Definition of Pubertal Onset in Girls

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Pelvic ultrasonography (US) is a quick, non-invasive and low-cost method, and doppler analysis facilitates assessment of flow impedance measurement in the uterine vascular tree. The pulsatility index (PI) reflects blood flow impedance in the vessel distal to the sampling point and has been suggested as a parameter to define pubertal development. In order to evaluate the PI and US measurements of uterus and ovaries in girls with different pubertal stages, we performed a cross-sectional study in girls with normal pubertal development. US and Doppler assessed PI of the uterine arteries (defined as the difference between the peak systolic flow and end-diastolic flow divided by the mean maximum flow velocity), endometrial thickness, uterine and ovarian volumes were evaluated. All the US exams were performed with the same equipment by the same radiologist. Clinical data such as the age of menarche, pubarche and thelarche were recorded. Statistical analyses were performed in SPSS, with ANOVA test, Spearman correlation and ROC curve with Youden. One hundred and sixty-nine girls aged 5-16 years (mean 11.3 ± 1.8) who performed two hundred and two pelvic US were included (Tanner 1=20%, Tanner 2=22%, Tanner 3=23%, Tanner 4=17%, Tanner 5=17%). Mean age of thelarche, pubarche and menarche were 11.1 ± 1.8, 10.2 ± 1.2 and 12.2 ± 1.1 years respectively. Prepubertal girls (Tanner 1) had mean PI significantly higher than girls in initial puberty (Tanner 2 and 3 grouped) and in late puberty (Tanner 4 and 5 grouped), respectively 6.5 ± 2.27 vs. 4.15 ± 1.55 vs. 2.82 ± 1.06, p<0.001 for all the comparisons. ROC curve analysis demonstrated that the PI is able to identify the onset of puberty with an area under the curve of 0.80 ± 0.04, P<0.001, and a cutoff point of IP=5.05 presented a sensitivity of 0.77 and a specificity of 0.80 to identify the onset of puberty. When we combined the cutoffs of IP <5.05 plus uterine volume >3.75 cm^3, we found a sensitivity of 0.72 and specificity of 0.90 to detect puberty. We identified a strong negative correlation between PI and uterine volume (rs=-0.72, p<0.001) and a moderate negative correlation with endometrial thickness (rs=-0.68, p<0.001) and right (rs=-0.60, p<0.001) and left (rs=-0.59, p<0.001) ovarian volumes. In conclusion, we found a significant reduction of the PI during pubertal development, reflecting a progressive increase in blood flow to the uterus, which can be a valuable non-invasive and highly specific tool to confirm the onset of puberty.

Pediatric Endocrinology
DISORDERS OF PUBERTY

Exaggerated Premature Adrenarche in Boys: Comparative Study of a Therapeutic Intervention With the Aromatase Inhibitor Anastrozole Versus Morning Low Dose Hydrocortisone

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Background: In boys, idiopathic premature adrenarche (IPA) is defined as the appearance of pubic or axillary hair/odor before the age of 9 yrs, not due to pathology of the adrenal glands. Exaggerated Adrenarche (EXAD), occurring in 10-15% of children with IPA, is characterized by an elevated >10 DHEA/Δ4 ratio (theoretically indicating reduced 3-β-HSD activity) and accelerated bone age (BA) maturation, continuously increasing the projecting distance from the target height (TH) curve, beyond the one observed in the pattern of Constitutional Advancement of Growth (CAG), eventually leading to short stature (SS). It is traditionally successfully treated with a morning (6-8 am) low dose of hydrocortisone (8 mg/m^2) in order to reduce the androgens produced and delay BA progression, similarly to the standard treatment of non-classical (late-onset) CAH. Third generation aromatase inhibitors (AI) have been shown to delay BA by inhibiting the peripheral aromatization of androgens and are being widely used off-label to treat short SS in boys. **Aims:** To evaluate the effectiveness of the AI anastrozole in delaying BA in boys with EXAD. **Methods:** 39 boys with advanced BA and a predicted adult height (PAH) <170cm and > -1SDS from TH) were included. Group-A (n=28) received anastrozole 1mg x 1 p.o. and group-B (n=11) low dose (8 mg/m^2) hydrocortisone at 6-8 am for at least 3 yrs. All measurements were made on the same height meter by the same examiner. The two groups did not differ in terms of age at intervention onset: 8.6 in group A vs 8.74 yrs in group B, TH: 175.7 vs 175.7 cm, PAH: 168.4 vs 167.8 cm and BA advancement: +2.3 yrs in group A vs +2.4 yrs in group B. A 6-month follow-up included clinical examination, BA assessment, and laboratory tests (general blood, lipid chart, LH, FSH, TESTO, E2, E1, and complete calcium metabolism). Lumbar spine DEXA scan and X-Ray was performed on an annual basis. **Results:** Both groups