Clinical case: An 11-year-old male initially seen at the PCP office for tachycardia and chest discomfort, especially during school exercise. He reported shortness of breath. His symptoms will resolve at rest. He was diagnosed initially with asthma and was put on Singular, Pulmicort, and albuterol as needed. His symptoms did not improve with this treatment, and he reported symptoms worsened with albuterol. He had a normal Echocardiogram and chest X-ray. A mild goiter was noted on his physical exam. Thyroid ultrasound showed an enlarged thyroid gland. An ovoid echogenic focus in the inferior thyroid lobe measuring 4 X 7 X 8mm was identified. The nodule was wider than tall, with a solid appearance with no internal color flow. Evaluation in our clinic showed normal TSH at 1.624mcIU/mL (0.35-5.5). FT4 was high at 1.54ng/dL (0.82-1.40), and FT3 elevated at 6.3pg/mL (3.3-4.8). Thyroid antibodies and thyroid-stimulating immunoglobulin (TSI) were normal. A 24 hour I-123 thyroid uptake was approximately 55% (10-30%) with no focal increased or decreased uptake. Given his elevated thyroid hormone levels with unsuppressed TSH in the context of goiter and tachycardia, genetic testing for the Thyroid receptor gene was done. He was found to be heterozygous for a pathogenic variant in THRB, c.1286G>A (p.Arg429Gln). This genotype is consistent with a diagnosis of autosomal dominant Thyroid hormone resistance. The patient was started on Atenolol, given his elevated heart rate, and he reported improvement in his symptoms during exercise.

Conclusion: Thyroid hormone resistance was first described as a clinical entity in 1967. The phenotype can vary among individuals. It is characterized by a reduced responsiveness of target tissue to thyroid hormone and binding affinity. The disease can present with goiter, behavioral issues, abnormal growth, and tachycardia. Affected individuals may have attention deficit-hyperactivity disorders (ADHD) and language difficulties. Thyroid hormone resistance can be misdiagnosed, as in our patient. He was diagnosed with asthma and was put on unnecessary medications that worsened his symptoms. Thyroid hormone resistance can also be misdiagnosed with Graves' disease, given the elevated thyroid hormone. It is essential to highlight the importance of genetic testing in these cases, as an accurate diagnosis will prevent unnecessary treatments with potentially serious side effects.

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PEDIATRIC ENDOCRINOLOGY CASE REPORT

Variable Clinical Presentation of Children With Hereditary Hypophosphatemic Rickets With Hypercalciuria: A Case Series

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Background: Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) is a rare condition of phosphate wasting due to variants in the SLC34A3 gene, encoding the sodium-phosphate cotransporter 2c (NaPi2c) at the brush border of proximal renal tubular cells (1). While labs are characterized by low serum phosphorus, high 1,25 dihydroxyvitamin D and inappropriately high levels of urine phosphate and calcium, the presenting symptoms can vary widely. Little remains known about specific phenotype-genotype correlations, especially in children. **Clinical Cases:** We report three new cases of HHRH in an unrelated 12 year-old male, 9 year-old female and 14 year-old male. All three patients were found to have low serum phosphorus for age (2.9-3.2 mg/dL), normocalcemia (9.4-9.9 mg/dL), low to low-normal parathyroid hormone (7-15 pg/mL), elevated 1,25 dihydroxyvitamin D (91-178 pg/mL), and hypercalciuria (4.5-7.6 mg/kg/day). Urine phosphorus was inappropriately elevated given the degree of their hypophosphatemia. Despite having similar lab findings, however, their clinical presentations were varied. The 12 year-old male presented with lower extremity pain, which was previously ascribed to patellofemoral pain syndrome. He had no history of renal symptoms, though a renal ultrasound later identified stones bilaterally. Conversely, the 9 year-old female and 14 year-old male presented with recurrent urinary stones and no bone symptoms. Genetic analyses identified 4 novel SLC34A3 gene mutations. Of interest, the 12 year-old male and 9 year-old female each shared a variant (c.575C-T (p.Ser192Leu)) despite having disparate symptoms. All three patients were treated with phosphorus supplementation and were advised to discontinue Vitamin D, if this had previously been prescribed. **Conclusion:** These three cases highlight the variability of presenting signs and symptoms among individuals with HHRH. Obtaining an accurate diagnosis is critical, as the addition of Vitamin D can seriously worsen symptoms in HHRH though it is a commonly used treatment for other disorders of phosphate wasting and bone demineralization. To aid in clinical decision making, we present a stepwise approach to the diagnosis of hypophosphatemic diseases.

References: (1) Lorenz-Depiereux, B., Benet-Pages, A., Eckstein, G., Tenenbaum-Rakover, Y., Wagenstaller, J., Tiosano, D., Gershoni-Baruch, R., Albers, N., Lichtner, P., Schnabel, D., Hochberg, Z., Strom, T. Hereditary Hypophosphatemic Rickets with Hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. Am. J. Hum. Genetic. 2006;78:193-201.

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PEDIATRIC ENDOCRINOLOGY: ADRENAL, THYROID, AND GENETIC DISORDERS

Antenatal Markers Related to Fetal Growth Restriction Can Predict Childhood Systolic Blood Pressure

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Background: Being born small for gestational age (SGA) is linked with higher systolic blood pressure (SBP). Fetuses with growth restriction (FGR) may be either SGA or appropriate size for gestational age at birth. However, it is not known which factors contributing to size at birth influence the relationship with SBP. **Aim.** To determine whether antenatal markers of FGR can predict the upper quartile of

childhood SBP. **Methods:** Brachial SBP was measured for 75 children aged 3-6 years from the Manchester BabyGRO Study, using a Tensiomed®Arteriograph with a child-sized cuff. SBP quartiles were generated. Participants were born to mothers who had attended a specialised clinic, following identification of higher FGR risk based on abnormal maternal serology (pregnancy associated plasma protein-A, β-human chorionic gonadotrophin, α-fetoprotein, Inhibin-A). Antenatal ultrasound data at 23 weeks gestation were obtained. Uterine artery Doppler (UtAD) notching was assigned a rank (0=absent, 1=unilateral, 2=bilateral). Random forest (RF) is a machine learning approach that generates many independent, uncorrelated decision trees based on multiple variables. This was used to determine the relative importance of antenatal variables in prediction of upper quartile of childhood SBP. Variables included in the model were maternal body mass index (BMI), parity, ethnicity (black/white/asian/mixed), maternal SBP and diastolic BP (DBP), maternal serology relating to FGR risk, UtAD pulsatility index, resistance index and notching rank (all measures of uteroplacental blood flow resistance), placental size measurements, 23 week estimated fetal weight (EFW) centile, Δ23w EFW-birthweight centile and birthweight SDS. A receiver operating characteristic (ROC) curve was generated, providing an area under the curve (AUC). A variable of importance (VIP) score was calculated for each marker that was significant in the model. All analyses were conducted in R (version 3.6). **Results:** RF analysis demonstrated antenatal markers relating to FGR risk predict the upper quartile of childhood SBP with an AUC 0.97. The top five ranked variables were maternal DBP (VIP score 14.0), birthweight SDS (11.5), parity (9.9), notching rank (9.5) and Δ23w EFW-birthweight centile (9.1). **Conclusion:** Maternal and antenatal markers, as well as birthweight SDS are linked with the upper quartile of SBP at 3-6 years. Antenatal markers were within the top five ranked and could help identify those babies at risk of higher SBP in childhood.

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PEDIATRIC ENDOCRINOLOGY: ADRENAL, THYROID, AND GENETIC DISORDERS

Are Current Normal Values of 11DOC Useful for Diagnosis of Non Classical Congenital Adrenal Hyperplasia Due to 11β- Hydroxylase Deficiency?

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Background: A non-classic form of 11β-hydroxylase deficiency (NC 11β-OHD) has been reported to cause mild androgen excess, with a clinical presentation of precocious puberty, menstrual cycle abnormalities, or hirsutism during adolescence. Since genetic diagnosis of NC 11βOHD is yet not routinely available, the current gold standard for biochemical diagnosis is elevated 11 DOC levels after corticotropin stimulation test (ACTHstimT). However, there are no clear hormone level cutoffs. One of the accepted references for basal and stimulated levels for the pediatric population was published in 1991 by Lashansky et al[1]. **Aim**: To determine the correlation between 11DOC levels measured during ACTHstimT, clinical symptoms attributed to NC11βOHD and androgen levels at presentation, and long-term follow-up among children and adolescents with hyperandrogenism. **Methods:** a retrospective study including all patients who underwent ACTHstimT between 20072015, in one center, during which 11 DOC levels were routinely measured as part of the test. Clinical data was collected from the patients' medical files and, by telephone calls for complete long-term follow-up. 11DOC levels before and after ACTHstimT were categorized as elevated according to both pre-defined cut-offs; greater than 1.5 times the 95th percentile according to Lashansky[1] normal level for sex and age, and greater than 1.5 times the upper limit of the normal level of the commercial kit. **Results:** Data were complete at presentation for 136 patients, 92 females, and for long for 98 patients, 68 females, mean follow up duration of 3.1 years (1.37,5.09). There was no statistically significant difference in the number of cases with elevated 11DOC according to both cut-offs, among patients with precocious and early puberty, premature adrenarche nor acne. Higher baseline and stimulated 11 DOC levels were demonstrated in females who presented with mild hirsutism and regular menses. Long term data demonstrated no statistically significant difference in the number of cases with elevated 11DOC levels among patients with compromised final adult height, PCOS or hyperandrogenism. There was negative correlation between stimulated 11 DOC levels and basal levels of testosterone, androstenedione and DHEAS levels. **Conclusions**: This report demonstrates that the current interpretation of 11DOC levels, basal and ACTHstimulated in children, according to 1.5 times the highest range, of both, the Lashansky[1] acceptable norms for children, and some of the laboratory's kit, are not clinically applicable.

[1]Lashansky G, Saenger P, Fishman K, Gautier T, Mayes D, Berg G and Reiter E. Normative data for adrenal steroidogenesis in a healthy pediatric population: Age- and sex-related changes after adrenocorticotropin stimulation. J. Clin. Endocrinol. Metab. 1991; 73(3): 674-686.

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PEDIATRIC ENDOCRINOLOGY: ADRENAL, THYROID, AND GENETIC DISORDERS

Associations of Size at Birth and Metabolic Syndrome Antecedents With Serum Spexin Levels in Prepubertal Children

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Background: Spexin is a novel peptide implicated in food intake and obesity. The primary aim of this study was to analyze whether serum spexin levels, along with total leptin and active ghrelin levels were different in prepubertal children born small for gestational age(SGA)