and nausea. These SX are attributed to impaired flow of CSF leading to benign intracranial hypertension (BIH). Occasionally, PTs with CM may require growth hormone therapy (GHT). This can potentially increase CSF accumulation and risk of BIH. The literature is limited to a small number of case reports on GHT in PTs with CM. Here, we describe the incidence of neurologic SX in 15 PTs.

Methods: Our database was queried for PTs with CM who were treated with GHT from 2010–18 and records were reviewed for adverse events. PTs with neoplastic disease, active inflammation, or acute trauma were excluded. CM was defined as cerebellar tonsils located below the foramen magnum on MRI.

Results: Mean and median ages of the 15 PTs (10 male, 5 female) who met inclusion criteria were 15.3 and 11.7 years, respectively. 14 were diagnosed as Type 1 and 1 was diagnosed as Type 2 CM. Tonsillar displacement ranged from 2-21mm, but was not specified in 5 PTs. Indications for GHT included isolated GH deficiency, panhypopituitarism, and chronic renal disease. Duration of GHT ranged from 0.2 to 12.25 years with a mean and median of 3.7 and 1.75 years, respectively. 7% (1 of 15) PTs experienced new-onset SX of BIH that could be attributed to GHT.

8 PTs (53.3%) did not experience any SX consistent with CM before, during, or after GHT. 3 PTs (20%) experienced neurologic SX prior to GHT. 1 PT reported diplopia and abnormal sleep patterns prior to GHT that resolved and did not recur during GHT. 1 PT prior to GHT manifested papilledema, 1 seizure, central sleep apnea, and occipital HA that resolved after posterior fossa decompression. Post-operatively and during GHT, this PT developed and continued to manifest nonpathologic pseudopapilledema. 1 PT continued to have pre-existing seizures and insomnia that did not worsen with GHT. 1 PT (7%) had congenital neurologic abnormalities in addition to CM. This PT had surgery to alleviate BIH caused by congenital hydrocephalus and SX permanently resolved. GHT has been continuous since birth with no new manifestations of CM reported post-operatively. 2 PTs (13%) developed new-onset neurologic SX while on GHT. 1 PT with diabetes experienced HA, 1 report of loss of consciousness, and 1 instance of apnea during periods of hyperglycemia. It was determined that these SX were unrelated to BIH and GHT was not interrupted. 1 PT experienced mild HA and 1 episode of occipital pounding with emesis during GHT. These SX resolved without intervention and GHT was continued without interruption. Despite the complexity of these cases, 0 PTs discontinued GHT.

Conclusion: Our study demonstrates that in a majority (93%) of cases, GHT does not cause onset or worsening of SX of BIH in PTs with complicated and uncomplicated CM. GHT should be regarded as a safe treatment in these PTs.

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS I

A Novel IGSF1 Variant in a Boy with Central Hypothyroidism and Epiphyseal Dysplasia

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SAT-057

Background: IGSF1 deficiency syndrome, also known as X-linked central hypothyroidism and testicular enlargement (CHTE) syndrome, is caused by mutations in the immunoglobulin superfamily, member 1 gene. Recently recognized as the most common genetic cause of isolated central hypothyroidism (CH), its cardinal features include CH and adult macroorchidism. We describe a boy with CH and epiphyseal dysplasia found to have a novel IGSF1 variant.

Clinical case: A male with attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, obsessive compulsive disorder and obesity was evaluated at age 9y for high total and LDL cholesterol and low T4 with normal TSH. He had short stature for family, high BMI, high sitting height ratio, and short arm span. Laboratory investigation revealed persistently mildly high total and LDL cholesterol, low T4, normal cortisol response to low-dose Cortrosyn stimulation, and normal IGF-1 and IGF-BP3. Bone age at 9y1m chronological age was 8y0m. Skeletal survey showed abnormal epiphyses of the femoral heads, knees, and humeral capitella suggesting primary epiphyseal dysplasia; he was referred to genetics. Growth improved after starting levothyroxine for CH. Multiple epiphyseal dysplasia gene panel (with reflex to clinical exome) did not find any variants known to be pathogenic for his condition. He was found to be a carrier of autosomal recessive Bartter syndrome. Heterozygous variants of unknown significance were found in RMRP, FGFR1, CDT1 and APOB. Whole exome sequencing showed hemizygosity for the p.Q743X (c.2227C>T) variant in IGSF1.

Discussion: The p.Q743X IGSF1 variant has not been reported in the literature and is not present in population databases. It is predicted to cause loss of normal protein function and is considered pathogenic. CH is found in all males with IGSF1 deficiency syndrome. Macroorchidism, another defining feature, develops in adulthood; age of testicular growth onset is normal, but pubertal testosterone rise is delayed. Our patient remains prepubertal at age 11y. Other features sometimes present include hypoprolactinemia (which was found in this child) and transient partial GHD (not seen in this case). Overweight and the metabolic syndrome are common; this child's cholesterol abnormalities may be due to weight and/or APOB variant found on genetic testing. ADHD has been seen in some patients with this syndrome; this child also has extensive psychiatric/behavioral problems, which have not been described. The skeletal findings in this case have not been previously noted in IGSF1 deficiency syndrome; whether this is a rare feature of IGSF1 deficiency syndrome or a separate entity is unclear. This case adds to the growing list of disease-causing variants in IGSF1. Endocrinologists should consider IGSF1 deficiency syndrome when diagnosing isolated CH in boys, as the characteristic macroorchidism is not present in childhood.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

Androgen Actions in Adipose Tissue and the Brain Are Key Mediators in the Development of Polycystic Ovary Syndrome

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SAT-018

Polycystic ovary syndrome (PCOS) is a complex disorder characterised by endocrine, reproductive and metabolic abnormalities. Despite PCOS being the most common endocrinopathy affecting women of reproductive age, its etiology is poorly understood so there is no cure and symptom-oriented treatment is suboptimal. Elucidation of the underlying mechanisms involved in the pathogenesis of PCOS would pave the way for the development of new interventions for PCOS. Hyperandrogenism is the most consistent feature observed in PCOS patients, and recently aberrant neuroendocrine signalling and adipose tissue function have been proposed as playing a pathogenic role in the development of experimental PCOS. To investigate the role of adipose tissue and the brain as potential key sites for androgen receptor (AR)-mediated development of PCOS, we combined an adipocyte and brain-specific ARKO knockout (AdBARKO) mouse model with a dihydrotestosterone (DHT)-induced mouse model of PCOS. Wildtype (WT) and AdBARKO prepubertal mice were implanted with a blank or DHT implant and examined after 12 weeks. In WT control females, DHT exposure induced the PCOS reproductive traits of cycle irregularity, ovulatory dysfunction and reduced follicle health. In contrast, these reproductive features of PCOS were absent in DHT-treated AdBARKO females. The PCOS metabolic characteristics of increased adiposity, adipocyte hypertrophy and hepatic steatosis were induced by DHT in WT females. Despite DHT treatment, AdBARKO females displayed normal white adipose tissue weight, and adipocyte hypertrophy and hepatic steatosis were not evident. However, as with WT mice, DHT treatment induced increased fasting glucose levels in AdBARKO females. These results demonstrate that adipose tissue and the brain are key loci for androgen-mediated actions involved in the developmental origins of PCOS. These findings support targeting adipocyte and neuroendocrine AR-driven pathways in the future development of novel therapeutic strategies for PCOS.

Neuroendocrinology and Pituitary

NEUROENDOCRINE & PITUITARY PATHOLOGIES

Interleukin-2 Administration in Healthy Men Activates Cortisol Secretion in an Age-, Dose-, and Body Composition-Dependent Way.

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SUN-309

Context. Interleukin-2 (IL2), a proinflammatory cytokine, is used for treatment of malignancies. Increased cortisol and ACTH were noted, but not investigated in detail. This is the first study in healthy men which uses moderate high IL2 doses as used in cancer treatment.

Objective. The goal of this study was to quantify cortisol secretion after a single sc injection of IL2 at 1900 h in young and older healthy men in relation to dose, age and body composition. **Design.** This was a placebo-controlled, blinded, prospectively randomized cross-over study in 17 young subjects (mean age 24.1 yr, range 19–30 yr) and 18 older subjects (mean age 63.9 yr, range 60–75 yr). The subjects underwent 24 h of blood sampling at 10-min intervals, starting at 1800 h. At 2000 h IL2 (3 or 6 million units per m^2 body surface) or saline was injected sc. Lights were off between 2300 and 0700 h.

Setting. The study was performed in a Clinical Translational Research Unit.

Outcome measures. Mean concentrations of cortisol, deconvolution analysis, and approximate entropy. Abdominal visceral fat (AVF) and total abdominal fat (TAF) were calculated from single slice CT.

Results. Cortisol concentrations started to rise at 2300 h. The AUC's during the lights-on periods were unchanged by IL2. Therefore, most analyses were restricted to the 8 h lights-off period. In young volunteers pulsatile cortisol secretion increased from 52.9±5.8 to 77.0±8.0 µg/L/8h and in older subjects from 60.6±3.8 to 70.6±4.6 µg/L/8h (GLM: treatment P <0.0001, treatment x age: P=0.02, mean ± SEM). Thus, the effect was smaller in older subjects. Increasing the IL2 dose increased cortisol secretion in young subjects (P= 0.001), but not in older subjects (P=0.90). In addition, the slopes (mean ± SE) of the linear part of the concentration curves after IL-2 were steeper than after placebo, pointing to accelerated release (young 1.40±0.13 to 3.76±0.11, P<0.0001, in older 1.27±0.04 to 3.28±0.15, P<0.0001).The incremental nocturnal pulsatile cortisol secretion after IL2 was negatively related to body composition (AVF: R=–0.41, P=0.019; TAF R=–0.41, P=0.043). Nocturnal ApEn-cortisol did not increase after low dose IL2 (0.981± 0.099 to 0.991±0.046, P=0.92). After high-dose, ApEn increased from 0.877±0.041 to 1.024±0.049, P=0.008, not correlated with body composition, nor with age. The ApEn increase points to decreased secretory regularity imposed by enhanced CRF signaling, rather than diminished cortisol feedback, which leads to greater secretory regularity.

Conclusion. Il2, a paradigm for inflammation, increased pulsatile cortisol secretion, more in young than in older subjects. Higher IL2 doses in young subjects amplified cortisol secretion, but not in older subjects. Cortisol secretion exhibited an advance (earlier) time shift, accompanied by accelerated secretion. Incremental nocturnal cortisol secretion was negatively related to fat mass.

Neuroendocrinology and Pituitary

CASE REPORTS IN NEUROENDOCRINOLOGY BEYOND THE PITUITARY

SDHD Mutation: Nonfunctional Paragangliomas Presenting as Bilateral Carotid Body Tumors with Syncope

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