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SUN-725

Context: The clinical recognition of familial central precocious puberty (CPP) has significantly increased in the last years. This fact can be related to the recent descriptions of genetic causes associated with this pediatric condition, such as loss-of-function mutations of two imprinted genes (*MKRN3* and *DLK1*). Inherited defects in both genes cause paternally inherited CPP. However, no genetic abnormality has been described in families with maternally inherited CPP so far.
Objectives: To characterize the clinical and genetic features of several families with maternally inherited CPP.
Setting and Participants: We analyzed clinical and genetic features of children with familial CPP. No brain MRI alterations were detected in the selected patients with CPP. *MKRN3* and *DLK1* pathogenic mutations were excluded. Whole-exome sequencing was performed in selected cases.
Results: We studied 177 children from 141 families with familial CPP. Paternal inheritance was evidenced in 44 families (31%), whereas 58 (41%) had maternally inheritance. Indeterminate inheritance was detected in the remaining families. Maternally inherited CPP affected mainly female patients (69 girls and two boys). Thelarche occurred at mean age of 6.1 ± 1.9 years in this female group. Most of girls had Tanner 3 (41%) and Tanner 4 (35%) breast development at first evaluation. One boy had additional syndromic features (macrosomia, autism, bilateral eyelid ptosis, high arcade palate, irregular teeth and abnormal gait). The pedigree analysis of patients with maternally inherited CPP revealed the following affected family members: 42 mothers, 10 grandmothers, 11 sisters, 12 aunts, and 11 female cousins. Most of the families (41) had two affected consecutive generations, while eight families had three affected generations. No consanguinity was referred. Ongoing molecular analysis revealed two rare heterozygous variants in the boy with syndromic CPP and three affected family members with precocious menarche (mother, maternally half-sister, and maternally aunt): a frameshift deletion (p.F144fs) in *MKKS*; and a missense variant (p.P267L) in *UGT2B4*, which encodes a protein involved in estrogen hydroxylation and it was related to menarche timing in genome-wide association studies.
Conclusions: Maternally inherited CPP was diagnosed mainly in girls, who had thelarche at mean age of 6 years old. Dominant pattern of inheritance was more prevalent, with direct maternal transmission in 72% of the studied families. New candidate genes might be implicated with maternally inherited CPP.

Thyroid

THYROID DISORDERS CASE REPORTS II

Response to Tocilizumab Retreatment in Refractory Thyroid Eye Disease

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SAT-500

Background: The current standard of care for moderate to severe thyroid eye disease (TED) is intravenous methylprednisolone (IVMP), though alternative immunosuppressive options are emerging. In a recent randomized trial, Tocilizumab (TCZ), an anti-IL-6 receptor antibody, demonstrated improved efficacy for corticosteroid-resistant TED compared to placebo. Clinical response to TCZ retreatment, however, has not been previously reported.
Clinical case: A 64-year old man presented with progressive diplopia, eyelid retraction and edema and retrobulbar pain. Initial labs revealed TSH 0.221 uIU/mL, free thyroxine (FT4) 1.11 ng/dL, total T3 172 ng/dL and a thyroid stimulating immunoglobulin (TSI) index of 329 (normal < 140). The patient was a former cigarette smoker who had recently transitioned to e-cigarettes. He was treated with 12 weeks of IVMP with improvement in ocular redness and swelling. Three months following completion of treatment, he presented with worsening left sided proptosis, restrictive strabismus, and compressive optic neuropathy (CON) evidenced by deteriorating central acuity and color vision. He underwent urgent surgical decompression for CON with full restoration of visual acuity. He then received a second 12-week course of IVMP with concomitant orbital radiation. Of note, his hyperthyroidism was well controlled with methimazole. Two months after his second IVMP course, he had a third flare of ophthalmic symptoms. He was then treated with TCZ 8 mg/kg (800mg) IV monthly for six months. The patient's Clinical Activity Score (CAS) improved from 4 to 2 and TSI index decreased from 610 to 92 (normal). He had significant improvement in periorbital edema, caruncle/plica swelling, and conjunctival injection. However, ten months following completion of the TCZ course he again complained of worsening diplopia and left proptosis. Of note, relapse of his TED symptoms was preceded by an increase in TSI from 92 to 300 two months prior. Orbital CT demonstrated progression of left orbitopathy and increased orbital apex crowding. Following these CT findings he was restarted on TCZ, of which he has now completed 5 additional infusions. His CAS has improved from 3 to 2 and TSI index has decreased from 284 to 100.
Conclusion: This is the first reported case of response to successive courses of TCZ in relapsing, severe, corticosteroid-resistant TED. TCZ can be an effective option for refractory TED though retreatment may be necessary for recurrent inflammation. Further study of TCZ is required to determine its role in relapsing TED and the optimal duration of therapy needed.
References:
Perez-Moreiras et al., 2018. Efficacy of Tocilizumab in patients with moderate to severe corticosteroid resistant Graves' orbitopathy: a randomized controlled trial. Am J Ophthalmol 195:181

Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

Prenatal Anti-Mullerian Hormone (pAMH) Exposure in Mice Induces Changes in Pubertal Onset, Fertility, and Stress Response in Both Male and Female Offspring

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MON-039

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility, classically presenting with disrupted ovulation, polycystic ovaries, and androgen excess, as well as many non-reproductive comorbidities. For instance, PCOS patients exhibit increased stress reactivity and higher rates of depression and anxiety compared to the general population. The prenatal anti-Mullerian hormone (pAMH)-induced model of PCOS was recently shown to recapitulate reproductive phenotypes in female mice, however little remains known about the consequences of pAMH exposure. We first aimed to expand upon this model by investigating pAMH-induced effects on offspring of both sexes. Pregnant dams on a C57Bl/6 background received daily i.p. injections of either AMH (0.12 mg/kg/d) or VEH late in gestation. Offspring were born into 4 groups (pAMH vs. VEH females, pAMH vs. VEH males) and assessed starting at weaning for changes in body weight, anogenital distance, pubertal onset, estrous cyclicity, fertility, and reproductive senescence. Statistical differences were determined by t-test or 2-way ANOVA when applicable, and significance set at $p<0.05$. As expected, pAMH increased anogenital distance in females but not males. Pubertal onset was delayed not only in females as previously reported, but also in males. Additionally, pAMH adult females showed significant disruptions in estrous cycling at P60 (increased time spent in diestrus, decreased number of cycles, increased cycle length), only mild disruptions by P90, then robust disruptions at 8 mo, 10 mo, and 12 mo of age that were distinct from reproductive senescence. When paired with wildtype untreated mates for a fertility assay starting at 3 mo of age, pAMH females had smaller and fewer number of litters, while pAMH males showed only delayed plugging behavior. Although pAMH males showed no difference in testis weight, pAMH females also had significantly reduced ovarian and uterine weights in diestrus. Interestingly, during the fertility assay, we found increased fetal death from both the pAMH females and males, even though pAMH males were paired with wildtype untreated females. We hypothesized that the increased fetal death could be the result of an pAMH-induced stress phenotype in both sexes. Using a simple stress response test measuring defecation and urination during exposure to a novel environment, we found that pAMH robustly increased stress response in both sexes at multiple timepoints. We also assessed glucocorticoid response to a restraint stress paradigm in adult females. While we observed no differences in baseline serum corticosterone levels, the pAMH group showed increased peak levels followed by a prolonged elevation levels after 2 hr. Together, these results enhance existing knowledge of the effects of pAMH exposure by demonstrating alterations in both male and female mice on both reproductive and non-reproductive measures.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Optimization of Experimental Conditions for Mimicking Hypoxia in Cultured Breast Cancer Cells by Using Cobalt(II) Chloride ($CoCl_2$)

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SAT-124

Hypoxia is a common phenomenon in solid tumor development caused by a decrease in either oxygen concentration or oxygen pressure as a result of rapid tumor cell growth. Hypoxia is characterized by stabilization of the alpha subunit of the hypoxia-inducible factor (HIF-1α) and its nuclear translocation and heterodimerization with HIF-1β. Activation of this signaling pathway involves multiple downstream effectors including carbonic anhydrase 9 (CA9, *s.* CAIX). A reliable method to mimic hypoxia utilizes cobalt(II) chloride ($CoCl_2$), which directly induces the expression of HIF-1α. The aim of this study was to optimize the experimental conditions for $CoCl_2$ treatment of breast cancer cells *in vitro* using three human breast cancer cell lines (MDA-MB-231, T-47D, and MCF-7 cells). We performed time- and concentration-response experiments, using various concentrations of $CoCl_2$ (50, 100, 200, and 300 μM) for 24 and 48 hours, and measured the expression of HIF-1α and CA9 by qRT-PCR and Western blot analyses. Results demonstrated that $CoCl_2$ downregulated HIF-1α mRNA levels but upregulated CA9 mRNA levels in a concentration- and time-dependent manner. Concomitantly, $CoCl_2$ treatment resulted in a significant induction of HIF-1α protein levels. We further investigated the effect of the $CoCl_2$ concentrations listed above on cell apoptosis using an *in situ* apoptosis detection kit. The results demonstrated that concentrations of $CoCl_2$ up to 100 μM had no significant effect on cell apoptosis.

Neuroendocrinology and Pituitary

PITUITARY TUMORS: TRIALS AND STUDIES

Intrapatient ACTH Variability in Cushing's Disease: Prognostic Significance

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OR23-01

Introduction: In patients with Cushing's Disease (CD), intrapatient variability of hormone measurements creates significant clinical challenges, therefore multiple measurements are recommended.[1] Urinary and salivary cortisol variation has been well described. However, intrapatient variation of adrenocorticotropic hormone (ACTH) in CD remains unknown. In CD patients, ACTH levels are inherently elevated from baseline but the coefficient of diurnal variation is reduced.[2]Additionally, at each diurnal time point, these exists a significant variation around the mean for the ACTH levels. In this study, we first analyzed the intrapatient variablility of ACTH at each diurnal timepoint in patients with CD. CD is primarily a disorder of ACTH excess, and treatment directed at pituitary adenomas would presumably perturb ACTH levels prior to affecting serum or urine cortisol. We hypothesized that the coefficient of variation at each diurnal time-point can help predict remission from CD following surgery.