was treated with supportive care and glucocorticoids with resolution of hypercalcemia and improved cardiac function. Unfortunately, serum 1,25 dihydroxy vitamin D was not successfully measured until after the first dose of prednisone and was found at the upper limit of our reference range 62.0 pg/mL (19.9-79.3).
Conclusion:
Immune checkpoint inhibitors are effective agents in treating various cancers. Adverse effects due to autoimmunity are common and early recognition of life-threatening complications is critical. Although cutaneous and pulmonary sarcoidosis have been described with ICI, to our knowledge, this is the first case report of ICI-related cardiac sarcoidosis presenting with PTH-independent hypercalcemia.

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

Characterization of the Adrenal Gland and Adrenal Rest Tissues in Congenital Adrenal Hyperplasia

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MON-171

Background: Adrenonodular hyperplasia and tumor formation are common long-term complications of congenital adrenal hyperplasia (CAH) driven by chronic ACTH elevation. Clinical studies indicate that the majority of males with classic CAH have testicular adrenal rest tumors (TART). Ovarian adrenal rest tumors (OART) are less commonly observed. Little is known about the pathophysiology of adrenal rest, however both adrenal cortex and Leydig cell markers have been described in TART, suggesting a pluripotent embryological cell origin.
Objective: To characterize adrenals and adrenal rest tissues of patients with CAH in comparison with normal tissues.
Materials and Methods: Using immunohistochemistry (IHC) and, real-time qRT-PCR we investigated CAH-affected adrenals (n=5), adrenal rest tissues (n=2; 1 testicular, 1 ovarian), controls [normal adrenal (n=2), testis (n=1), and ovary (n=1)]. Tissue sections prepared from paraffin embedded tissue blocks were immunostained with adrenal [melanocortin 2 receptor (*MC2R*), delta-like homolog 1 (*DLK-1),* steroidogenic factor 1 (*SF-1*), steroidogenic acute regulatory protein (*StAR*) and other cytochrome P450 genes], inflammatory [interleukin 2 receptor *(IL-2R)*, B-lymphocyte antigen (*CD20)*, cluster of differentiation 3 (*CD3)*, tumor necrosis factor alpha (*TNFα),* interleukin 6 *(IL6)*], and gonadal markers [progesterone receptor (*PR*), androgen receptor (*AR*), insulin-like 3 (*INSL3)*]. RNA was isolated and gene expression studies were performed. High-throughput RNA sequencing technology was used to analyze the differential transcriptome profiles between the CAH adrenals, adrenal rest and normal tissues.
Results:
In contrast to the controls, CAH adrenals and adrenal rest tissues showed the following:
(i) IHC studies revealed 95% of tissue positive for adrenal zona-reticularis; (ii) significant nodular lymphocytic infiltration with a predominance of B and T lymphocytes and overexpression of lymphocyte markers *IL-2R, CD20, CD3,* and inflammatory cytokines *TNFα and IL6;* (iii) increased expression of adrenocortical specific genes *MC2R, DLK1.*
Conclusion: CAH-affected adrenals and adrenal rest tissue have similar predominance of zona reticularis and demonstrate lymphocytic infiltration. Active inflammation may play a role in the abnormal development of adrenal and adrenal rest tissue in CAH patients.

Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

Brain Aromatase Is Essential for Regulation of Sexual Activity in Male Mice

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OR09-03

Introduction: The biologically active form of estrogen, estradiol (E_2), has important organizational roles in brain development and activational roles in adult brain physiology and behavior. It has been proposed that E_2 formation in the brain might regulate sexual activity in various species. The mechanisms that link estrogen formation in the brain and sexual behavior, however, remain unclear. Aromatase is the key enzyme that catalyzes the conversion of testosterone (T) to E_2 in the testis and brain of male mice. To determine the role of brain aromatase in male sexual activity, we generated a brain-specific aromatase knockout (bArKO) mouse model. Additionally, a newly generated total aromatase knockout (tArKO) mouse model served as a positive control. *Methods:* We generated the floxed aromatase mice ($Arom^{fl/fl}$), which flanked the transcription and translation start sites and the common splice acceptor site for the upstream brain promoter I.f of the aromatase gene. We then crossed Nestin-Cre mice with $Arom^{fl/fl}$ mice to generate bArKO mice. Using the same $Arom^{fl/fl}$ mice, we bred tArKO via crossing with ZP3-Cre mice. Circulating and tissue (brain and testis) E_2 levels were measured using liquid chromatography-tandem mass spectrometry. We assessed sexual activity in 12-14 week-old bArKO, tArKO and littermate control males over two 30-minute trials. The interactions were monitored and videotaped, and the videotape was scored for the sexual activity. To investigate whether the lack of estrogen production in the brain was causative for altered sexual behavior, 20 bArKO and 20 control mice were castrated at ~nine weeks of age and supplemented with exogenous sex hormone via 60-day time release pellet implantation. *Results:* E_2 levels are significantly decreased in the brain but not the testis of bArKO

mice as compared to control mice (P < 0.05, n=6-12). As expected, E_2 levels in the brain and testis are significantly lower in tArKO mice compared with their WT littermates (n=6-9). Furthermore, we demonstrate that local aromatase expression and estrogen production in the brain is required for male sexual behavior and sex hormone homeostasis. Male bArKO mice exhibited significantly decreased sexual activity in the presence of strikingly elevated circulating T (n=5). In castrated adult bArKO mice, administration of E_2 together with T restored maximum sexual behavior (n=5). Thus, aromatase in the brain is necessary for T-dependent male sexual activity. We also found that brain aromatase is required for negative feedback regulation of circulating T of testicular origin. *Conclusion:* Our findings suggest T activates male sexual behavior in part via conversion to E_2 in the brain and provide the foundation for inhibition or enhancement of brain aromatase enzyme activity and/or utilization of selective estrogen receptor modulators in modifying sexual behavior.

DCB and HZ contributed equally to this work.

Adrenal

ADRENAL CASE REPORTS I

Silent Pheochromocytoma Complicated by Adrenal Insufficiency After Unilateral Adrenalectomy

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SAT-184

Background: Adrenal insufficiency (AI) following unilateral adrenalectomy for pheochromocytoma (PCC) is an exceedingly rare occurrence described previously in 1 study in only 4 out of 13 patients with unilateral PCC. We discuss an unusual case of a patient with incidentally discovered PCC who underwent unilateral adrenalectomy and subsequently developed AI.

Clinical Case: 61-year-old male in overall good health taking no medications presented with left flank and groin pain after a handlebar injury in a bicycle crash. CT angiogram Abdomen & Pelvis revealed a complex enhancing left adrenal mass with internal necrosis measuring 13 x 12 cm. He denied history of headaches, diaphoresis, chest pain or hypertensive crisis. He did endorse palpitations which had resolved with reduced caffeine intake. Labs showed plasma free metanephrine 3,295 pg/mL (ref range <57) and normetanephrine 68,472 pg/mL (<148), 24hr urine metanephrine 192,677 ug (52-341), 24hr urine normetanephrine 171,880 ug (88-444), 24hr urine vanillylmandelic acid (VMA) 182 mg (1.8-6.7), serum aldosterone 8.1 ng/dL (<39.2), serum free cortisol 0.47 ug/dL (0.07-0.93), 24hr urine cortisol 41.6 ug (<60), DHEA sulfate 37 ug/dL (42-290). He was started on phenoxybenzamine and underwent left adrenalectomy. Of note patient remained only minimally hypertensive with tumor manipulation intraoperatively. Pathology was consistent with PCC with no evidence of regional or distant metastases. Postop-labs showed plasma free metanephrine <25 pg/mL and normetanephrine 122 pg/mL. Calcitonin and parathyroid hormone levels were normal. Patient was evaluated in endocrinology clinic 4 weeks after surgery for complaint of severe fatigue, weight loss, anorexia and myalgias. Adrenocorticotropic hormone (ACTH) level was 31 pg/mL (7.2-63) with AM cortisol of 2.1 ug/dL (5-23) which increased to 7.4 ug/dL 1 hour after Cosyntoprin 250 mcg stimulation. He was started on prednisone 10 mg once daily with significant improvement in his symptoms.

Conclusion: PCCs typically manifest as sustained or paroxysmal hypertension, episodic headaches, palpitations or diaphoresis. Our patient was found to have a PCC with strikingly elevated levels of catecholamines without typical signs and symptoms of PCC. To the best of our knowledge this is the 5th reported case where a patient developed AI after unilateral adrenalectomy for PCC. There are case reports describing PCCs which secrete both catecholamines and ACTH. However, our patient lacked clinical or biochemical evidence of hypercortisolism preoperatively and his tumor cells in path sample stained negative for ACTH. Other possible pathophysiologic mechanisms include ectopic corticotropin releasing factor production leading to subclinical Cushing syndrome (SCS). Clinicians should have a high suspicion for SCS in the setting of PCC to promptly diagnose and treat AI after unilateral adrenalectomy.

Thyroid

THYROID AUTOIMMUNITY AND BENIGN THYROID DISEASE

Effect of Teprotumumab on Proptosis Reduction Across Various Demographic Sub-Groups

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OR18-01

Introduction: Teprotumumab, an insulin-like growth factor 1 receptor inhibitory monoclonal antibody, was recently shown to significantly reduce proptosis in patients with active, moderate-to-severe thyroid eye disease (TED) in phase 2 and phase 3 clinical trials.[1,2] Prior analyses have demonstrated a combined trial proptosis response (≥2 mm reduction) rate of 77.4% in the teprotumumab group and 14.9% in the placebo group after 24 weeks of therapy (p < 0.001).[3] The current analysis was performed to investigate whether or not patient demographic characteristics influence the teprotumumab proptosis response.

Methods: Data from two 24-week randomized, double-masked, placebo-controlled, parallel-group, multicenter studies (Phase 2 [NCT01868997], Phase 3 [NCT03298867[) were combined. All patients had active TED associated with Graves' disease. The study eye designated at baseline manifested more severe TED and a clinical activity score of > 4. Subjects were divided into subgroups based on gender, smoking status, and age at baseline (younger: <65, older: ≥65). The percentage of proptosis (≥2 mm) responders and proptosis change from baseline were examined in each of these subgroups. Because most of both teprotumumab (85%) and placebo (87%) subjects were white, there were