TC by immune-enzymatic assay at 8 AM following overnight administration of 1 mg dexamethasone at 11pm. Subjects were excluded if they had a known adrenal adenoma, any form of endogenous cortisol excess, or exogenous steroid use. **RESULTS:** DST was performed in 165 healthy volunteers, median age of 29.5 (18-74) years; 53 men (32%) and 112 (67%) women, median BMI 25 (18-42) kg/m^2, 47 (42%) of which were taking OCT (median daily ethinylestradiol dose of 30 (20-35) mcg). The median DEXA was 0.34 (0.09-1.12) mcg/dl, median TC was 0.8 (0.25-15.7) mcg/dl and median FC was 24 (4-714) ng/ml. TC and FC measurements were highly correlated (r^2=0.89, p<0.0001). The median FC/TC was 3% (0.3-6.7), lowest in women on OCT (median 2.5% vs 3.3% in women not on OCT and men, p<0.0001). TC>1.8 mcg/dl was demonstrated in 18 (11%) healthy subjects (men: 3/53, 5.7% vs women not on OCT: 3/65, 4.6% and women on OCT: 12/47, 25.5%, p=0.0007). Excluding women on OCT, the proportion of subjects with TC>1.8 was higher when DEXA was <0.2mcg/dl (4/15, 27%) vs when DEXA was >0.2mcg/dl (2/101, 2%),(p<0.0001). After excluding 24 (14%) healthy subjects with DEXA <0.2 mcg/dl, in the remaining 142 subjects (51 (35%) men, 54 (38%) women not on OCT and 39 (27%) women on OCT), median TC was 0.75 (0.25-4.6) mcg/dl and median FC was 23 (4-103) ng/ml). Significant differences were noted in both TC and FC following DST within subgroups: men vs women not on OCT vs women on OCT, TC: 0.6 vs 0.7 vs 1.3 mcg/dl, (p<0.0001) and FC: median 20 vs 22 vs 31 ng/ml, (p<0.0001). All men and all women not on OCT demonstrated post-DST FC <50 ng/ml (97.5% cutoff of 47 and 37), while women on OCT demonstrated post-DST FC <50 in 80% and FC<75 in 95%. **CONCLUSION:** Post-DST TC>1.8 mcg/dl was demonstrated in 11% of all healthy subjects, of which 1 in 4 were women on OCT and 1 in 4 had DEXA<0.2 mcg/dl. Simultaneous measurement of serum DEXA during DST may be valuable when false positive results are suspected. Despite a lower FC/TC ratio in women on OCT, post-DST FC cutoffs were higher in women on OCT. Measurement of FC after DST may be helpful in some but not all women on OCT.

Neuroendocrinology and Pituitary

CASE REPORTS IN UNUSUAL PATHOLOGIES IN THE PITUITARY II

A Rare Case of Pituitary Aspergillosis Diagnosed by CSF PCR in an Immunocompetent Patient with Headaches and Photophobia

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Background: Pituitary aspergillosis is a rare infection usually found in the immunocompromised population. It is oftentimes mistaken for a pituitary adenoma based on similar clinical presentation and characteristic findings on MRI. Most cases require removal of the pituitary mass in order to make a diagnosis. Here we present the case of an immunocompetent patient with headaches and photophobia diagnosed with pituitary aspergillosis by CSF PCR and treated medically with voriconazole.

Clinical Case: A 40-year-old woman with a questionable history of Brucellosis presented with a 3 month history of headaches along with 2 days of nausea and vomiting. Vital signs were notable for intermittent hypotension but were otherwise within normal limits. Physical exam was notable for tenderness at the left temporal region, diaphoresis and photophobia. Patient was otherwise alert and oriented and had no visual field deficits or extraocular muscle dysfunction.

Patient was found to have central adrenal insufficiency with undetectable AM cortisol (<0.5 mcg/dL, n 3.7-19.4 mcg/dL), inappropriately normal ACTH (7 pg/mL, n 6-58 pg/mL) and central hypothyroidism with low TSH (0.057 mcIU/mL, n 0.358-3.8 mcIU/mL) and low free T4 (0.48 ng/dL, n 0.76-1.46 ng/dL). Patient initially presented with hyponatremia (Na 119 mmol/L, n 137-145 mmol/L) likely secondary to central adrenal insufficiency and central hypothyroidism. Gadolinium-enhanced pituitary MRI showed a heterogeneous 1.8 cm pituitary mass with rim enhancement concerning for hypophysitis.

Patient was started on stress-dose steroids with IV hydrocortisone 100 mg IV q8h, levothyroxine 50 mcg PO daily and empiric antibiotic therapy with ceftriaxone, doxycycline and rifampin due to suspicion for neurobrucellosis. Lumbar puncture was obtained showing low glucose (39 mg/dL, n 40-70 mg/dL), normal protein (47 mg/dL, n 12-60 mg/dL) and an elevated white count (WBC 9/mcL, n 0-5/mcL) with lymphocyte predominance (97% lymphocytes, n 40-80%). Blood and CSF cultures showed no growth at 2 weeks. CSF was sent for multiplex PCR which came back positive for *Aspergillus*.

Patient was discharged with voriconazole 300 mg PO BID for 1 year, levothyroxine 75 mcg PO daily and hydrocortisone 10 mg PO Qam and 5 mg PO Qpm. Three months later, repeat MRI showed resolution of the pituitary mass and patient felt well without headaches, nausea or vomiting.

Conclusion: This case demonstrates an atypical example of pituitary aspergillosis diagnosed without pituitary mass biopsy and treated medically with voriconazole. It demonstrates the possible role of CSF PCR to diagnose the condition and guide antifungal treatment.

Tumor Biology

NOVEL REGULATORS OF BREAST CANCER PROGRESSION

Steroid Receptor Co-Activators Complexes Cooperate with Progesterone Receptors (PR) to Reprogram Metabolic Pathways that Drive Therapy Resistant Populations in ER+ Breast Cancer

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Late recurrence of metastatic disease stemming from acquired therapy resistance remains a significant health burden for women with ER+ breast cancer. Disseminated ER+ tumor cell populations can remain quiescent for years to decades, and contributing factors include breast cancer stem cells (CSCs), which are non-proliferative and frequently exist as a minority population in recurrent

therapy-resistant tumors. Progesterone receptors (PR) are known drivers of normal stem and breast CSCs. Our objective was to define novel signaling pathways governing cell fate transitions involved in driving therapy resistance in ER+ breast cancer. We reported that cytoplasmic complexes composed of steroid receptor (SR) co-activators, PELP1 and SRC-3, drive breast CSC outgrowth. SRC-3 knockdown abrogated PELP1-induced CSC expansion and target genes required for cell survival, suggesting an essential role for PELP1/SRC-3 complexes. PELP1 also forms a signaling and transcriptional complex with ER and PR-B. Phospho-PR species are key mediators of stemness in ER+ breast cancer models. Accordingly, PR knockdown and antiprogestins disrupted PELP1/SRC-3 complexes and blocked PELP1-induced breast CSC outgrowth. Mammary stem cell (MaSC) populations were increased *in vivo* in MMTV-tTA;TRE-cyto-PELP1 transgenic mice as well as in MMTV-tTA;TRE-hPR-B mice. To better understand PELP1-mediated pathways, we performed RNA-seq on MCF-7 PELP1+ models grown in tumorsphere conditions to enrich for CSC populations (ALDH+, CD44+/CD24-). Cytoplasmic PELP1-expressing cells had a different global gene profile relative to WT PELP1 (i.e. nuclear). Gene sets associated with stem cell biology, hypoxic stress, and cancer metabolism were differentially regulated, including members of the glycolytic bi-functional kinase/phosphatase PFKFB family. Seahorse metabolic phenotyping demonstrated cytoplasmic PELP1 influences metabolism by increasing both glycolysis and mitochondrial respiration. Cytoplasmic PELP1 interacted strongly with PFKFB3 and PFKFB4, and inhibition of PFKFB3 or PFKFB4 kinase activity blocked PELP1-induced tumorspheres and protein-protein interactions with SRC-3. Additionally, antiprogestin and PFKFB inhibitors were synergistic when combined with ER+ targeted therapies. These aspects of PELP1/SRC-3 biology were phenocopied in therapy resistant models (tamoxifen resistant [TamR], paclitaxel resistant [TaxR]). Together, our data suggest that PELP1, SRC-3, PR, and PFKFBs form complexes that reprogram cellular metabolism to drive breast CSC expansion. Identifying the mechanisms that regulate recurrent ER+ tumor cell populations will enable specific targeting within heterogeneous breast tumors and may lead to the development of non-ER targets that can be used in combination with endocrine treatments to overcome therapy resistance.

Adrenal

ADRENAL MEDICINE — CLINICAL APPLICATIONS AND NEW THERAPIES

Morning ACTH Levels as a Reliable Biomarker for Excluding Autonomous Cortisol Secretion in Incidetally Discovered Adrenal Adenomas. A Prospective Cohort

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Adrenal incidentalomas are common with a prevalence of 3-10% and in up to 30% of cases may have probable autonomous cortisol secretion. Hypercortisolism is associated with substantial cardiometabolic morbimortality and can physiologically decrease ACTH levels.

Objective: To determine the sensitivity, specificity, and positive and negative predictive values of ACTH levels in evaluating autonomous cortisol secretion in a prospective cohort of incidentally discovered adrenal adenomas.

Methods: We prospectively evaluated 224 consecutive adult subjects with incidentally discovered adrenal masses on computed tomography. Finally, 168 participants with radiographic adenoma criteria underwent systematic hormonal assessment, including measurements of morning cortisol and ACTH on day 1, and a 1 mg dexamethasone suppression test (DST) on day 2. Hypercortisolism was excluded if the DST was < 1.8 mcg/dL. Autonomous cortisol secretion was defined as a DST > 5.0 mcg/dL and DST levels of 1.8-5.0 mcg/dL were considered to be possibly autonomous hypercortisolism. We evaluated the correlation of ACTH levels with clinical, radiographic, and endocrine variables. In order to identify the most sensitive threshold value for diagnosing autonomous cortisol secretion, we determined ROC curves and negative likelihood ratio (NLR). Concordance of repeated ACTH was assessed using Bland Altman analysis.

Results: The characteristics of the cohort were mean age 56 (+/- 11.8) years, 76% female, adenoma size 19 (+/- 7) mm, and 13% bilateral adenomas. Mean ACTH was 15 (+/- 11) pg/ml (range 5-72) and the mean DST was 2.2 (+/- 3.0) ug/dL (range 0.4-25.9). Fifty-four (32%) participants had a DST ≥1.8mcg/dL and 13 (8%) a DST≥5.0 mcg/dL. We found no correlation between ACTH levels and age, gender or body mass index. ACTH was inversely associated with adrenal adenoma diameter (r=-3.3 p=0.002) and volume (r=-2.9 p=0.008). There was an inverse association between ACTH and DST values (r=-3.1 p=0.01). In the subgroup of patients with a second ACTH measurement we found high concordance, with mean difference of 0.16+/-3.6 pg/ml (p=0.83). ROC analysis showed that an ACTH ≥20 pg/ml had a sensitivity of 98% to exclude hypercortisolism, with a negative predictive value of 97% and a negative likelihood ratio of 0.06. The only case with DST≥1.8 and ACTH≥20 had Cushing´s phenotype with both an adrenal adenoma and a pituitary ACTH-producing adenoma. Systematic evaluation of morning cortisol and ACTH allowed the detection of 5 cases of false negative low DST values due to the use of non-oral corticosteroids.

Conclusion: In this cohort, an ACTH ≥20pg/ml excluded autonomous cortisol secretion with excellent sensitivity and negative predictive value, providing strong reassurance that there is no clinically relevant hypercortisolism. Therefore, subjects with a normal DST and ACTH ≥20pg/ml should be candidates for relaxed surveillance.

Thyroid

THYROID DISORDERS CASE REPORTS I

Rapid Resolution of Hyperthyroidism Induced Hepatic Dysfunction with Methimazole

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