SAT-479

INTRODUCTION:

Classically, cardiac tamponade presents with hypotension, distant heart sounds and tachycardia (Beck's triad). Pericardial window is considered effective treatment. Pericardial effusions are relatively common in hypothyroidism (3-6%) (1). Cardiac tamponade, however, is rarely seen in patients with hypothyroidism secondary to pericardial distensibility and the slow accumulation of fluid, allowing significant fluid accumulation without hemodynamic compromise (2).

CLINICAL CASE:

A 84 year-old female with history of post-surgical hypothyroidism (on levothyroxine 150 mcg) following total thyroidectomy for thyroid cancer, cardiac tamponade requiring pericardial window formation two years prior, presented for dyspnea on exertion and pedal edema for several days. She was tachypneic to 22/min with heart rate 47/min and blood pressure 92/62. Distant heart sounds were noted on exam.

EKG demonstrated sinus bradycardia, low voltage QRS and T wave flattening. Further workup revealed TSH elevated to 44 uIU/mL (N:0.27–4.2 uIU/mL), free T4 0.17 ng/dl (N:0.93-1.7 ng/dl) and undetectable T3 (N: 80-100 ng/dl). Echocardiogram unexpectedly demonstrated a large circumferential pericardial effusion with diastolic collapse of the right atrial, right ventricular free wall, significant respiratory variations and interventricular dependence. These findings were consistent with cardiac tamponade physiology. She underwent a video assisted left thoracotomy pericardial window formation along with drainage of 400cc of yellow pericardial fluid. Fluid cytology and tissue histopathology were negative for malignancy. Her uncontrolled hypothyroidism was considered the cause for recurrence of cardiac tamponade and her levothyroxine dose was increased to 175 mcg. At two week follow up, she reported symptomatic improvement on the higher levothyroxine dose. Echocardiogram did not show reaccumulation of fluid.

CONCLUSIONS:

Sinus tachycardia is found in most patients with cardiac tamponade, except in hypothyroid patients (2). A high degree of suspicion is needed to diagnose cardiac tamponade in hypothyroidism, even in patients who have undergone presumed definitive therapy with a pericardial window in the past. The recent onset of pedal edema and low blood pressure were important indicators of impending cardiac compromise in our patient.

Hypothyroid patients may be at higher risk of pericardial window failure compared to patients with cardiac tamponade of other etiologies, especially if thyroid replacement therapy is inadequate. The scientific literature is lacking in this regard and warrants further investigation.

References:

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Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

Dissecting the Relative Role of Estrogen and Androgen in Fibrosis, Skeletal Muscle Atrophy, and Inguinal Hernia Formation

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SAT-736

Introduction: More than one in four men develop symptomatic inguinal hernia, and hernia repair is the most commonly performed general surgical procedure in the US. Despite its prevalence, the molecular mechanisms causing inguinal hernia remain unclear. Aromatase, the key enzyme for the conversion of testosterone (T) to estradiol (E2), is present in human but not mouse skeletal muscle tissue. We recently demonstrated that robustly increased local E2 levels in lower abdominal muscle (LAM) tissue and decreased circulating T levels were associated with fibrosis and myocyte atrophy in LAM tissue, leading to severe scrotal (inguinal) hernia formation in a humanized aromatase transgenic mouse model ($Arom^{hum}$) with a high LAM human aromatase expression. To further determine the relative role of estrogen and androgen in the development of inguinal hernia, we generated a novel mild $Arom^{hum}$ mouse model with lower LAM aromatase expression compared with the severe model. *Methods:* Mild $Arom^{hum}$ mice were followed for 6 months to determine hernia incidence and measure hernia size (n=30). We treated mild $Arom^{hum}$ mice with the aromatase inhibitor, letrozole (n=12) for 12 weeks. Circulating and LAM E2 levels in mice were measured using mass spectrometry. LAM tissue fibrosis and myocyte size were determined by Masson's trichrome staining and H&E staining, respectively. *Results:* The mild $Arom^{hum}$ mice contain a single copy of the human aromatase genomic fragment with a truncated regulatory region, giving rise to significant but mildly elevated LAM E2 levels (2.5-fold) at 15 weeks of age. Interestingly, these mice maintain normal circulating T levels. Furthermore, we show that mildly increased LAM E2 without decreased circulating T levels cause hernia formation in about 88% of mild $Arom^{hum}$ mice in contrast to 100% hernia formation in mice containing the full-length human aromatase regulatory region (severe $Arom^{hum}$ model), suggesting that higher LAM estrogen and low serum T levels contribute to this severe phenotype. Treatment with an aromatase inhibitor restores LAM E2 levels to normal levels and completely prevents inguinal hernia formation in the mild $Arom^{hum}$ mice. In LAM fibroblasts of mild $Arom^{hum}$ mice, we find very high levels of estrogen receptor-α expression, which possibly mediates

estrogen-induced hernia formation. *Conclusion:* Taken together, our findings from the mild *Arom*^{hum} mouse model suggest that lower levels of estrogen excess in LAM are the primary driver of muscle atrophy and hernia formation because this mouse model do not exhibit circulating T deficiency. Our findings will constitute a starting point for dissecting the relative roles of estrogen and androgen action in inguinal hernia development. This has the potential to facilitate drug development to prevent and treat hernias, especially recurrent hernias after primary hernia repairs in vulnerable populations such as elderly men.

Neuroendocrinology and Pituitary
HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Food Restriction Effects on the Hypothalamus-Pituitary-Gonadal Axis

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SAT-290

It is well known that nutritional status affects the reproduction, since an adequate amount of energy is necessary for puberty onset and fertility. However, the neural mechanisms by which energy homeostasis affects reproduction is not completely elucidated. To determine if acute or chronic food restriction (FR) are able to modulate the estrous cycle, adult female mice were used in the experiments. The estrous cycle was evaluated by daily observation of vaginal smear. To determine the effects of an acute FR protocol on estrous cycle, females were individualized and kept on *ad libitum* diet (control, n=17) or fasted for 24 hours (n= 21). A subgroup of animals was euthanized shortly after the 24-hours test to collect hypothalamus and determinate *Kiss1* mRNA levels, while another group of mice were regrouped and fed *ad libitum*. To determine the effects of a chronic FR protocol on estrous cycle, control mice were individualized and maintained with 100% of daily food content (average of 5 g per day, n = 6), or submitted to 60% of FR (n= 12). Animals were fed *ad libitum* after test. As expected, mice fasted for 24-hours exhibited a significant weight loss (control: 21.7 g ± 0.5 vs 21.6 ± 0.5 g; fasted: 22.7g ± 0.5 vs 18.7g ± 0.4, *P*=0.0001). This effect was followed by a significant reduction of hypothalamic *Kiss1* mRNA expression (control: 1.0 ± 0.2; fasted: 0.3 ± 0.05, *P*=0.04, n=4/4 per group). Surprisingly, even under lower *Kiss1* mRNA levels, 24-hours fasting induced no changes on estrous cycle. On the other hand, chronic FR induced a gradual weight loss (body weight at the 5th day of FR, control: 21.5g ± 0.2; FR: 17.3g ± 0.7, *P*=0.0002). The chronic FR was follow by the disruption of estrous cyclicity. While control mice exhibited a regular pattern of cyclicity during the period of evaluation, only leukocytes were identified in the vaginal smear of mice submitted to 60% of FR, even though they had a normal cycling pattern before the test. Therefore, by comparing 30 days of estrous cycle evaluation, including the period before chronic FR, while control mice exhibited cornified cells in the vaginal smear 58.5 ± 4.9% of days, female mice submitted to FR exhibited cornified cells in 38.3 ± 3.8% of days (*P*= 0.0068). Approximately 3-4 days after the end of the chronic FR females returned to exhibit estrous cyclicity, however the length of the estrous cycle was prolonged compared to control group. Our data suggest that chronic nutritional status variations are required to disrupt the hypothalamus-pituitary-gonadal axis and therefore the estrous cyclicity.

Neuroendocrinology and Pituitary
NEUROENDOCRINE & PITUITARY PATHOLOGIES

The Interaction Between Thiazide-Associated Hyponatremia and Acute Illness in Hospitalised Patients

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SUN-306

Thiazide diuretics, widely used in the management of hypertension, are associated with a five times greater risk of hyponatremia (serum Na <135mmol/L) than in the general population. Hyponatremia in hospitalised patients warrants special consideration since it is associated with increased morbidity and mortality.

The aim of this study was to describe the clinical characteristics and outcomes in acutely ill medical patients with thiazide-associated hyponatremia (TAH).

We performed a retrospective, case control study examining all acute, unselected medical admissions, over a six week period, to The Royal London Hospital. Cases were defined as adults admitted to hospital with TAH (hyponatremia and a history of being prescribed thiazide diuretic pre-admission). Each case was matched by age, gender and degree of hyponatremia to a similar control - admitted with hyponatremia and no pre-admission exposure to thiazide (non-TAH). Clinical characteristics and treatment outcomes were compared between TAH and non-TAH cohorts.

A total of 1,341 consecutive acute medical admissions (49.7% men) were evaluated. Hyponatremia was detected in 240 (17.9%) admissions. Median (±SD) length of stay was longer among patients with hyponatremia compared to normonatremic patients (5.0±12.4 versus 3.0±9.2 days; p=<0.0001). In-hospital mortality was higher in the hyponatremic group (8.8% versus 4.4% p=0.005). Twenty-two cases (11 men) of TAH accounted for 9.2% of patients with hyponatremia. Median age 64±14 years was similar to other patients with hyponatremia 68±20 years. The median admission serum sodium for TAH cases was 131.5 mmol/L (IQR 126.8 - 134) with a discharge serum sodium of 136.5 mmol/L (IQR 133.8 - 139.3). When compared to matched controls, patients with TAH had similar presenting symptoms - most commonly confusion, headache and dizziness. Length of stay among TAH cases was similar to controls; 5.5±5.1 versus 4.0±3.7 days; p=0.24. Mortality (10%) was the same in both groups. Thiazide was withdrawn during admission in 14 (64%) cases.

In conclusion, acute, clinical outcomes for hospitalised patients with TAH are similar to those with comparable degrees of hyponatremia due to other causes.