have no response to high doses of injected human insulin, suggesting extreme insulin resistance. Cost limitations preclude optimal diagnostic evaluation. Empiric treatment with low cost options potentially may provide diagnostic information as well as efficacious treatment.

Thyroid

NO LONGER A PAIN IN THE NECK — RECENT INSIGHT INTO THYROID GROWTH, DEVELOPMENT, AND PATHOLOGY

Approaching Indeterminate Thyroid Nodules in the Absence of Molecular Markers. "The BETH-TR Score"

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OR28-05

Context: Given the lack of easy access to molecular markers, for indeterminate thyroid nodules (Bethesda (BETH) category III, IV), the clinician can either decide to get a second opinion from an expert high volume thyroid cytopatholgist, re-do the FNAC after a period of 3-6 months or send the patient for a diagnostic hemithyroidectomy. Reviewing the sonographic risk features is also one way of triaging these nodules. The ACR-TIRADS (TR) is an objective method of sonographic risk assessment and is superior to other forms of sonographic classification. **Aim**: We propose combining the scoring of TR category and BETH category (both expressed as numerical value and summated) and look at the score which could potentially guide the clinician in deciding whom to send for surgery. **Settings and Design**: Observational Prospective collection of consecutive patient data from Thyroid FNAC clinic. **Statistical analysis used**: The BETH categories were represented numerically and summated with the TR category. The categorical outcome variables of Benign and Malignant nodules and the summated score was analysed using Kruskal-Wallis test. **Results**: We analysed 450 FNAC data, out of which 403 were thyroid nodule aspirates. Out of these nodules, 96 of them underwent surgery and 64% of these nodules were malignant on final histopathology (Malignant=62 and Benign=34). The mean (sd) size of the benign nodules was 3.6 (2.2)cm compared to 2.8 (1.8)cm of the malignant nodules. After excluding those with BETH 1 (n=4), the mean BETH-TR score for benign nodules was 6(1.4) and malignant nodules 9.4(2.1) ($p<0.0001$). The BETH-TR score progressively increased from 7.3(0.92) in Follicular thyroid cancers (FTC) to 8.6(1.4) in Follicular variant Papillary thyroid cancer (FVPTC) to 10(1.3) in classic Papillary thyroid cancers (PTC). Among the indeterminate nodules (BETH III & IV; n=40), the BETH-TR score of benign nodules was 6.75(1) and malignant nodules was 7.5(0.72) (p value=0.01). A BETH-TR score >=7 gave a sensitivity of 92% specificity of 74% and correctly identified malignant nodules in 86% of cases (Likelihood ratio 3.5; ROC area: 0.8841; CI 0.79-0.94). **Conclusion**: A combined sonocytological BETH-TR score is one way to triage management of indeterminate thyroid nodules. A BETH-TR score >=7 gave a sensitivity of 92% specificity of 74% and correctly identified malignant nodules in 86% of cases.

Thyroid

NO LONGER A PAIN IN THE NECK — RECENT INSIGHT INTO THYROID GROWTH, DEVELOPMENT, AND PATHOLOGY

Constitutive Activation of NRF2 Antioxidant Response Leads to Age-Dependent Goiter and Compensated Hypothyroidism in Male Mice.

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OR28-01

Background: Familial non-toxic multinodular goiter (MNG) is a rare disease. *KEAP1* gene (Kelch-like ECH-associated protein 1) that encodes the main inhibitor of nuclear factor erythroid 2-related transcription factor 2 (Nrf2), a central mediator of antioxidant responses, has been found to be one of the mutated genes that lead to familial MNG. The proposed association of *KEAP1* with familial MNG is based on only two loss-of-function mutations in respective Japanese families, only one of which included proper phenotyping and demonstration of co-segregation of phenotype and mutation. To date, there is no experimental evidence from model organisms to support that decreased Keap1 levels can cause goiter. **Hypothesis:** We hypothesized that enhanced Nrf2 signaling induced by loss of Keap1 function in mice can lead to goiter. **Methods:** To this end, male Keap1 hypomorphic C57BL/6J mice that express ~80% less Keap1 in their tissues (Keap1 knockdown mice:"Keap1KD") were studied at 3 and 12 months of age and compared to wild-type mice (WT). Plasma, thyroids and pituitary glands were collected for assessment of thyroid function by radioimmunoassays and for histology as well as gene and protein expression by quantitative PCR and immunoblotting respectively. **Results:** Keap1KD showed diffuse goiter that began to develop in early adult life and became highly prominent at the age of 12 months when the thyroids of Keap1KD were 6-fold heavier than WT. Histomorphometry assessment of thyroids showed that Keap1KD had ~3-fold larger follicle

area and colloid compartment but no thyroid nodules or hyperplasia was detected. Keap1KD also showed primary hypothyroidism already in early adult life that was eventually well-compensated over time by increased TSH levels (at age of 12 months: WT TSH=47.7±9.1 mU/L, Keap1KD TSH=460±74 mU/L). This was also reflected in the pituitary gland of Keap1KD where *Tshb* mRNA was ~3-fold higher than WT. Despite a known stimulatory effect of Nrf2 on Tg gene transcription and Tg protein abundance, these measures were decreased in the thyroid of Keap1KD mice. No clear patterns were observed in the expression profiles of other thyroid hormone synthesis-specific factors, such as *Duox1, Duoxa1, Duox2*, *Duoxa2, Tpo, Nis, Dio1, Dio2, Dehal1* mRNA levels, with the exception of Tg-processing and Tg-degrading cathepsins, including an increase in mature forms of cathepsins D, L and S. **Conclusions:** Keap1KD mice showed age-dependent diffuse goiter and compensated hypothyroidism. The precise mechanism accounting for the thyroidal phenotype remains to be elucidated, but it may involve enhanced Tg solubilization and excessive lysosomal Tg degradation. This study unravels novel roles of the druggable Keap1/Nrf2 pathway in thyroid function and economy. Subclinical hypothyroidism in Keap1KD mice may have broader implications regarding their use in metabolic research.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS I

Euglycemic Diabetic Ketoacidosis in Type 2 Diabetes Mellitus

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SAT-LB118

Introduction

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication of diabetes. It is characterized by the triad of hyperglycemia (>250mg/dL), high anion gap metabolic acidosis (HAGMA), and ketonemia. Rarely, it would present with normal or mildly increased glucose levels (<200mg/dL) making it a diagnostic challenge. We present a case of euglycemic DKA in type 2 diabetes mellitus (T2DM).

Case Presentation

A 77-year-old woman living in a nursing home with a history of T2DM treated with insulin glargine, but for the past three days refused medications with decreased caloric intake. There were no new medications or ingestion of alcohol or toxic substances. She then developed worsening altered mental status hence admission to the hospital. Her vital signs were within normal limits. Physical examination revealed no abdominal tenderness. Initial laboratory studies showed glucose 83 mg/dL, bicarbonate 10 mmol/L, and anion gap 23 meq/L. Urinalysis significant with trace ketones. The following day, further work-up was done remarkable with beta-hydroxybutyrate 8.3 mmol/L, lactic acid 0.8 mmol/L, and toxicology panel negative. Arterial blood gas showed pH 7.137, pCO2 14 mmHg, and bicarbonate 4.8 mmol/L. DKA protocol was initiated and she was treated with insulin drip, bicarbonate drip, and intravenous fluid administration with D5W. After two days, DKA resolved and was subsequently transitioned to subcutaneous insulin.

Discussion

Similar to the findings of Burge et al, our case showed that decreased caloric intake predisposes patients with diabetes mellitus to euglycemic DKA during periods of insulin deficiency. A proposed mechanism for the accelerated ketosis is due to the effects of elevated levels of glucagon or catecholamines on lipolysis. Other causes of euglycemic DKA include pregnancy, heavy alcohol use, SGLT2 inhibitors, cocaine abuse, pancreatitis, sepsis, and chronic liver disease. It is also important to rule out other causes of HAGMA. In our case, although she has decreased caloric intake, starvation ketoacidosis usually leads to serum bicarbonate levels >18mmol/L. Management is similar to DKA but important difference is the dextrose administration to prevent hypoglycemia.

Conclusion

Euglycemic DKA is a medical emergency that may be overlooked as patients present without marked hyperglycemia. Physicians should have a high suspicion as this may result in delayed management and potential adverse metabolic consequences.

Neuroendocrinology and Pituitary

CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

Chronic Opioid Use as a Cause of Severe Hypothyroidism: A Case Report

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SAT-LB45

Background: Hypogonadism and hypocortisolism are present in a sizeable proportion of chronic opioid users. (1) An association with hypothyroidism, however, has not been demonstrated.

Clinical Case: A 56-year old woman with chronic pain syndrome on opioids presented from a nursing home with decreased level of consciousness and was found to be hypotensive requiring ICU admission. Several weeks prior to her presentation, she was hospitalized for progressive weakness and was found to have evidence of panhypopituitarism: low TSH (0.209 uIU/mL, nl 0.400 – 4.200), low free T4 (0.76 ng/dL, nl 0.80 – 1.50), low LH (<0.12 mIU/mL, nl 10.9 – 58.6), low FSH (1.7 mIU/mL, nl 16.7 – 113.6), and abnormal ACTH stim test (ACTH 6.4 pg/mL, nl 7.2 – 63; cortisol 0-min 3.8 mcg/dL, nl 6.7 – 22.6; 60-min 13.10). She was discharged on levothyroxine 25 mcg daily and prednisone 7.5 mg daily. On admission, her exam was notable for symmetric, non-pitting edema of the lower extremities to the knees with peau d'orange appearance. Initial tests revealed profound hypothyroidism with low TSH (0.381 uIU/mL), low free T4 (0.60 ng/dL), undetectable total T4 (<0.9 mcg/dL, nl 5 – 12.2), and undetectable free T3 (<1.00 pg/mL, nl 2.5 – 3.9). Thyroglobulin and TPO