

identified a heterozygous novel *STAT5B* mutation by Whole Exome Sequencing (WES) in a 2.2-year-old boy who presented proportionate short stature (height -2.77 SDS) with mild immune dysregulation. He also had normal GH response to provocative tests, low IGF-I levels, and a limited response to IGF generation test. This variant is located within the highly conserved SH2 domain responsible for recognizing and interacting with tyrosine-phosphorylated target peptides. The aim of our study was to evaluate the functional consequences of this novel heterozygous human *STAT5B* variant (K632N), using the zebrafish as a biosensor system, to determine its pathogenicity. To do this, we performed overexpression experiments microinjecting construct-derived mRNA for the wildtype (WT) and mutant variant into zebrafish embryos at the 1-cell stage and assessed the consequences at 72 hours post fertilization (hpf). The missense variant was introduced into the full length *STAT5B* cDNA clone (Origene) by site-directed mutagenesis. To generate mRNA, WT and mutant forms of *STAT5B* cDNAs were linearized by digestion with XhoI, purified and subsequently transcribed with Mmessage Mmachine T7 Transcription Kit. Zebrafish embryos microinjected with 100 and 200 pg of mutant mRNA show a dose dependent significant reduction of body length at 72 hpf compared to those microinjected with the same dose of WT mRNA ($p < 0.001$). Body length reduction with 100 pg of mutant mRNA was 4%, while with 200 pg was 12.7% ($p < 0.001$). In addition, a significant number of embryos injected with mutant mRNA show developmental defects including pericardial edema, bent spine, and cyclopia compared to those injected with WT mRNA ($p < 0.001$). In the case of pericardial edema, the number of affected embryos increased significantly with the mutant mRNA dose ($p < 0.005$). In conclusion, our study was able to evidence the pathogenic nature of the *STAT5B* K632N variant since it leads to growth and developmental defects in zebrafish embryos. The zebrafish, and its conserved GH-IGF-I axis, constitutes an ideal *in vivo* model for characterizing the functional effect of genetic variants in ortholog human genes.

Diabetes Mellitus and Glucose Metabolism

TYPE 1 DIABETES MELLITUS

Acute Onset Type 1 Diabetes Mellitus Caused by the Checkpoint Inhibitor Nivolumab

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Background. Checkpoint inhibitors are monoclonal antibodies that augment immune system antitumor activity. Nivolumab is a checkpoint inhibitor that targets the programmed cell death receptor 1 (PD-1). Approximately 15% of patients treated with checkpoint inhibitors experience endocrine immune-related adverse events (irAEs),

with autoimmune thyroid disorders and hypophysitis the most common endocrine irAEs. We present a case of acute onset type 1 diabetes mellitus (T1D) complicating treatment with nivolumab.

Case. An 84 year old female received nivolumab (Opdivo) for metastatic small cell lung cancer. She tolerated twelve cycles of treatment well, but after the thirteenth cycle, she developed polydipsia and polyuria that prompted her to seek medical attention. Laboratories in the emergency department were notable for plasma glucose 998 mg/dL, bicarbonate 13 mM, anion gap 24, and strongly positive serum and urine ketones. An insulin infusion and parenteral fluids promptly resolved diabetic ketoacidosis (DKA), and the patient was then managed with subcutaneous basal/bolus insulin. Antibody markers (e.g. anti-GAD65) for T1D were undetectable, and evaluation for other endocrine irAEs was unremarkable. Given the rapid onset of DKA and the patient's advanced age, she was diagnosed with nivolumab-induced T1D and discharged home on exogenous insulin.

Conclusions. In a recent meta-analysis of 38 immune checkpoint inhibitor trials and over 7,500 patients, T1D was the least common endocrine irAE. The incidence of T1D was 0.2% compared to 6.6% for hypothyroidism, 2.9% for hyperthyroidism, 1.3% for hypophysitis, and 0.7% for primary adrenal insufficiency. All but one case (12/13) of T1D occurred in patients treated with a PD-1 inhibitor. Markers of both cellular and humoral diabetes-associated autoimmunity have been demonstrated in patients with T1D during treatment with nivolumab, and autoimmune destruction of beta-cells is the presumed etiology of diabetes. However, diabetes autoantibodies are detected in only about 50% of cases, and the absence of humoral markers does not exclude the diagnosis of nivolumab-induced T1D. There is a slight male predominance among published cases of nivolumab-induced T1D, and though median onset of T1D is after 11 weeks of treatment, there is a wide range of recorded times to T1D onset. Approximately 70% of patients present in DKA, and the significant majority of patients have undetectable or low C-peptide levels. Unfortunately, loss of beta-cell function persists after stopping nivolumab, and lifelong exogenous insulin is required for diabetes management. Though nivolumab-induced T1D is rare, the high risk of DKA as in this patient's case illustrates the importance of recognizing nivolumab as a potential cause of autoimmune diabetes in older patients receiving anti-PD-1 immunotherapy.

Reproductive Endocrinology

REPRODUCTIVE ENDOCRINOLOGY: REPRODUCTIVE FUNCTION AND DYSFUNCTION ON DEVELOPMENT

The Effect of Exercise Training on Reproductive and Cardiometabolic Outcomes in Women with Polycystic Ovary Syndrome: A Pilot Randomized Controlled Trial

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Exercise may improve cardiometabolic, reproductive and psychological outcomes in women with Polycystic Ovary Syndrome (PCOS). Clinical Practice Guidelines recommend exercise to treat PCOS, but the most effective exercise prescription is unclear. The aim of this randomized controlled trial was to evaluate the effects of six months of thrice weekly high-intensity interval training (HIIT) and continuous aerobic exercise training (CAET) programs compared with no exercise in previously-inactive women aged 18–40 years with PCOS. The primary outcome was change in ovulation rate. Ovulation was assessed with daily at home ovulation prediction kits, and confirmed with serum progesterone levels. Fisher's exact test was used to compare groups. Secondary outcomes included change in BMI, waist circumference, blood pressure, A1C, fasting glucose, fasting insulin, and lipids and were analyzed using repeated measures mixed models. 47 women were randomly assigned to no exercise control (n=17), HIIT (n=16), or CAET (n=14). 22/33 (66.7%) women ovulated during the intervention period: no exercise: 8/12 (66.7%), HIIT: 8/11 (72.7%), and CAET: 6/10 (60%); NS between groups. BMI decreased significantly in the CAET group compared with control (-1 kg/m^2 , $p=0.01$) and compared with HIIT (-0.9 kg/m^2 , $p=0.04$). Mean waist circumference decreased significantly in all groups with no significant difference between groups. There were no significant within- or between- group changes for body weight. No within- or between group differences were identified for mean blood pressure, A1C, fasting glucose, fasting insulin, or triglycerides. Mean LDL-C was significantly different between the HIIT and CAET groups (-0.33 mmol/L , $p=0.03$), as LDL-C decreased in the HIIT group but not in the CAET group. HDL-C increased in the HIIT group compared with the no exercise group (0.18 mmol/L , $p=0.04$), with no significant difference between the CAET and no exercise groups ($p=0.47$). In conclusion, CAET and HIIT interventions in women with PCOS did not affect ovulation rates. CAET and HIIT both were effective at improving anthropometrics and some cardiometabolic health markers in women with PCOS. Further studies are needed to determine optimal exercise prescriptions for reproductive, anthropometric and cardiometabolic outcomes in women with PCOS.

Neuroendocrinology and Pituitary

CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

Resolution of a Cystic Macroprolactinoma with Dopamine Agonist Therapy

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Background. Prolactinomas with cystic regions occupying $\geq 50\%$ of tumor volume are classified as cystic prolactinomas.

They appear to arise from tumor necrosis or hemorrhage. Though Pituitary Society guidelines recommend surgery as first-line treatment for cystic prolactinomas, there is evidence that cystic prolactinomas are hormonally and anatomically responsive to treatment with dopamine agonists (DA). We present a case of a cystic macroprolactinoma fully responding to treatment with cabergoline. **Case.** A 31 year old male was referred for evaluation of gynecomastia, diminished libido, and erectile dysfunction that occurred over the course of eight months. Bilateral glandular breast tissue with a slight right asymmetry was present. Testes were 15–20 mL, soft, and without masses. Phallus and pubic hair were unremarkable. Morning (8 AM) testosterone, estradiol, and LH levels were 92 ng/dL (348–1197), 13.4 pg/mL (7.6–42.6), and 2.0 mIU/mL (1.7–8.6), respectively. Prolactin level was 331 ng/mL (4–15), and MRI with pituitary protocol revealed a 1.4 x 1.0 x 1.5 cm cystic mass with peripheral rim enhancement and extension into the suprasellar cistern. No mass effect on the optic chiasm was observed. Somatotroph, thyrotroph, and corticotroph axes were unaffected. Cystic macroprolactinoma causing hyponadotropic hypogonadism complicated by gynecomastia was diagnosed. The patient chose initial management with cabergoline 0.25 mg twice weekly. Three months after starting treatment, libido and erectile function had recovered to baseline, 8 AM testosterone was 607 ng/dL, and hyperprolactinemia was well controlled (4.2 ng/mL). At six months, anatomic resolution of the cystic macroprolactinoma was demonstrated on repeat pituitary MRI. Plastic surgery was required for management of gynecomastia. **Conclusions.** Surgery is recommended for management of cystic prolactinomas due to concern that a lack of dopamine receptors in the cystic components of tumors will make DA ineffective reducing tumor size. However, this case joins a growing body of evidence that DA can treat hyperprolactinemia and induce regression of cystic macroprolactinomas. For example, in a retrospective case review of patients with cystic macroprolactinomas at Massachusetts General Hospital, persistent cyst reduction occurred in 20 of 22 patients treated initially with DA, and median reduction in cyst volume exceeded 80 percent. Median time to documented cyst reduction was approximately six months, and there was no difference in degree of cyst reduction for patients treated with bromocriptine or cabergoline. The response of cystic prolactinomas to DA is similar to solid prolactinomas, and DA are reasonable initial treatment for cystic macroprolactinomas without clear indications for surgery.

Thyroid**THYROID NEOPLASIA AND CANCER**

TRK-Fusion Thyroid Cancer: A Clinical Overview in a Large Population at a Single Cancer Center

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