increase in LI after ACTH to the group that had a decrease in LI, the latter had significantly higher rates of lateralization pre-ACTH (89% vs 74%, p=0.02) and significantly lower rates of lateralization post-ACTH (50% vs 78%, p=0.001). All of these general findings were validated in the separate cohort of 233 patients. The discordance rate between pre-ACTH lateralization and available imaging data was 32%; the same discordance rate was found when comparing post-ACTH lateralization to imaging.

Conclusions: The administration of ACTH during AVS causes an increase in LI in half of patients and a decrease in LI in the other half. Using conventional cut-offs, pre-ACTH and post-ACTH lateralization indices disagree on laterality more than 20% of the time and almost always involve pre-ACTH unilateral disease that is classified as bilateral disease post-ACTH. These findings underscore that while ACTH stimulation may be useful for confirming adrenal vein selectivity, the decrease in post-ACTH LI may result in misclassification of surgically curable primary aldosteronism in a substantial proportion of patients.

Neuroendocrinology and Pituitary

RESEARCH ADVANCES IN PITUITARY TUMORS

The Role of Germline Defects in Cushing's Disease

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J.L.M. and C.A.S. contributed equally. **Introduction:** Cushing's Disease (CD) has been described as a component of a number of familial genetic syndromes. Yet, such cases may go largely unrecognized due to phenotypic variability, incomplete penetrance, and the rarity of the disease. We determined the frequency and type of germline genetic causes of CD and characterized their clinical phenotype in a large cohort of CD patients. **Methods:** We studied 245 unrelated CD patients (139 females, 60.4%), referred to our Center between 1997–2018, including 230 pediatric (≤18 years at disease onset, 93.9%) and 15 adult patients (6.1%). Germline genetic causes were identified by whole exome sequencing in 184 patients and by Sanger sequencing of specific genes in 39 patients; 22 patients did not undergo genetic testing, due to low quality or insufficient DNA. When available (n=66), corticotropinoma DNA was screened for *USP8* hotspot variants using Sanger sequencing. **Results:** Eighteen patients (7.3%) had positive family history: nine presented as FIPA with unknown genetic cause, eight presented as MEN1 (seven had confirmed *MEN1* variants), and one had a family history of pheochromocytoma/paraganglioma and pituitary adenoma with unknown genetic cause. Among the 227 sporadic patients (92.7%), 13 (5.7%) simplex cases had putative pathogenic variants in the following genes: *CDKN1B* (n=5), *CABLES1* (n=3), *AIP* (n=1), *PRKAR1A* (n=1),*TP53* (n=1),*TSC2* (n=1), and *USP8* (n=1). Altogether, cases with potentially inheritable genetic causes(familial and simplex) accounted for 12.7% (31/245) of all patients. There were no statistically significant differences in age at disease onset, age at diagnosis or tumor diameter between patients with potentially inheritable genetic defects and the rest of the cohort. In the pediatric subset, however, there was a non-significant higher frequency of macroadenomas among familial and simplex patients (21.4%), compared with sporadic patients (12.4%, *P*=0.19). Somatic *USP8* hotspot mutations were found in 33.3% (12/36) of sporadic patients, but only in 3.3% (1/30) of familial and simplex (e.g. patients with a disease-associated germline defect, but no affected relatives) cases (*P*=0.0038). The global frequency of *USP8* defects was 19.7% (13/66). **Conclusions:** Potentially inheritable cases of CD accounted for one-eighth of the patients in our cohort: 64.5% (20/31) of them are associated with defects in genes with a known involvement in CD. Patients with germline genetic causes of CD might present as apparently sporadic cases, due variability in disease penetrance. Unlike sporadic cases, somatic *USP8* hotspot mutations are rare in those with inheritable causes of CD, suggesting different drivers for tumorigenesis in each group. Identifying the genetic causes of CD should lead to a more precise genetic testing and counselling and might aid in developing targeted therapeutic strategies.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

A Novel Human Heterozygous STAT5B Variant Leads to Impaired Growth and Developmental Defects in Zebrafish Embryos

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Signal transducer and activator of transcription 5b (STAT5b) has been identified as a key downstream mediator of GH signaling in somatic growth. Autosomic recessive human mutations in *STAT5B* lead to severe growth retardation associated to immune dysregulation. On the other hand, some heterozygous *STAT5B* mutations have been associated to a milder form of the disease. We have

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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SAT-673

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 T1D1 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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