and cardiovascular events. To date, there are no data on the prevalence and predictors of acute and perioperative complications in patients with active Cushing's syndrome.
Methods
In a single-center cohort analysis we evaluate predictors and outcomes of acute, life-threatening and perioperative complications in patients with active biochemically verified Cushing's syndrome attending our endocrine department between 1978 and 2016. Any medical complications necessitating hospitalization, including admission to intensive care units (ICUs), from the time of appearance of first symptoms of hypercortisolism until one year after biochemical remission by surgery (or where surgical remission was not achieved, during continuing follow-up) were recorded and classified. Baseline factors related to and predicting acute complications were tested using uni- and multivariate analysis.
Results
The study included 242 patients (m/f n=54/188) with Cushing's syndrome (pituitary n=99, adrenal n=116, ectopic n=27), 14.0% of which had malignant disease.
At least one acute complication was observed in 54.5% of patients; these included electrolyte disturbances (24.4%), infections (27.7%), thromboembolic events (14.9%), cardiac arrhythmias necessitating medical intervention (5.4%), hypertensive crises (8.7%), acute coronary events (3.3%) and cerebrovascular events (4.1%). At least one ICU admission (excluding post-surgical observance) was required in 13.2% of patients. The majority of complications occurred prior to surgery (60-90%); infections occurred pre- and postoperatively (51.7% vs 48.3%, respectively).
Patients with ectopic Cushing's syndrome demonstrated a higher likelihood of infection ($p<0.001$), hypokalemia ($p<0.001$) and ICU stays ($p=0.009$) compared to patients with pituitary or adrenal Cushing's syndrome. Patients with diabetes mellitus at diagnosis (n=81) had a significantly higher frequency of infection ($p<0.001$), hypokalemia ($p<0.001$), hypertensive crises ($p=0.004$), acute coronary events ($p=0.029$), arrhythmias ($p=0.025$) and a higher likelihood of an ICU stay ($p<0.001$).
The total number of acute complications and the number of days at ICU correlated positively with parameters of cortisol excess including urinary free cortisol and the time of hypercortisolism.
Conclusion
This cohort analysis identifies a significantly high prevalence of acute and perioperative complications in Cushing's syndrome, with one in eight patients suffering a life-threatening situation necessitating ICU admission. These acute complications are positively predicted by the degree of hypercortisolism, emphasizing the necessity for acute interventions aiming to reduce cortisol excess even before definitive disease cure is achieved.

Adrenal

ADRENAL CASE REPORTS I

Parotid Carcinoma Ex Pleomorphic Adenoma Can Produce Ectopic ACTH Too

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SAT-213

Background: Ectopic ACTH syndrome accounts for about 14% of Cushing syndrome cases. Small cell lung cancer is the most common cause. A few case reports described ectopic ACTH syndrome in patients with parotid acinic cell carcinoma. Parotid carcinoma ex pleomorphic adenoma is a malignant transformation within a pleomorphic adenoma, which is mostly adenocarcinoma not otherwise specified, but other subtypes can occur.
Clinical Case: A 41-year old man with parotid cancer and hypothyroidism was admitted to the hospital for hypokalemia (2.1 mmol/L, n: 3.5-5 mmol/L). Parotid cancer was diagnosed a year before admission. At that time, he underwent left parotidectomy, and pathology showed carcinoma ex pleomorphic adenoma with areas of acinic cell carcinoma. Despite chemoradiation, he was diagnosed with metastasis in the lungs, for which pembrolizumab was started. Over the two months prior to admission, he gained 20 lb, and developed lower extremity weakness, acne, erectile dysfunction and loss of libido. He was also diagnosed with hypertension and started to have mild hypokalemia. Suspecting hyperaldosteronism, oncology team ordered labs just prior to admission, which showed the hypokalemia of 2.1 mmol/L, hypernatremia (147 mmol/L, n: 133-143 mmol/L), normal aldosterone and renin, and high cortisol (59.12 mcg/dL, n: 3-22 mcg/dL) and ACTH (121 pg/mL, n: 9-50 pg/mL).
In the hospital, potassium was slowly improving despite aggressive replacement, and blood pressure was still elevated despite increasing his lisinopril dose. Screening for Cushing syndrome revealed an abnormal 1 mg dexamethasone suppression test (cortisol 51.9 mcg/dL, n: <1.8 mcg/dL), and high 24-hour urinary free cortisol (6495 mcg/24h, n: 3.5-45 mcg/24h) and midnight salivary cortisol (2610 ng/dL and 4250 ng/dL, n: <100 ng/dL). Cortisol was not suppressed after 8 mg dexamethasone (cortisol 47.85 mcg/dL, pretest cortisol 48.73 mcg/dL) pointing toward ectopic ACTH syndrome. Spironolactone was started and titrated up to 100 mg BID with better control of hypertension and normalization of potassium. Ketoconazole was started at 200 mg TID and increased gradually as outpatient to 400 mg TID within three weeks. A repeat 24-hour urinary free cortisol was done five weeks after ketoconazole was started showing significant improvement (110 mcg/24h, n: 3.5-45 mcg/24h). Potassium requirements remarkably decreased from 80 mEq TID to 40 mEq daily. Of note, chest CT done during hospitalization showed new lung lesions despite treatment with pembrolizumab.
Conclusion: This is the first case of ectopic ACTH syndrome to be described in a patient with parotid carcinoma ex pleomorphic adenoma, though areas of acinic cell carcinoma within the tumor can be the source of ACTH. Hypercortisolism due to ectopic ACTH secretion is usually of rapid onset, and can present with severe hypokalemia. Steroid synthesis inhibitors seem to be an effective therapy.

Genetics and Development (including Gene Regulation)

ENDOCRINE DISRUPTING CHEMICALS

Bisphenol-A Alters Pancreatic B-Cell Proliferation and Mass in an Estrogen Receptor Beta-Dependent Manner

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SAT-715

Bisphenol-A (BPA) is one of the highest volume chemicals produced worldwide. It is used as the base compound in the manufacture of polycarbonate plastics, epoxies and resins. Humans are consistently exposed to BPA and consistently it has been detected in the majority of individuals examined. Experimental research in animals, as well as human epidemiological studies, converge to conclude that BPA is a risk factor for the development of type 2 diabetes. In previous studies we have demonstrated that the exposure to BPA during embryonic development promote an increment of pancreatic β-cell mass. This was correlated with increased β-cell division and altered global gene expression in pancreatic β-cells. The aim of this work was to determinate whether ERβ was involved in the in the β-cell mass and proliferation increment observed in male mice offspring. ERβ+/- pregnant mice were treated with vehicle or BPA (10 μg/kg/day) from day 9 to 16 of gestation. Offspring pancreatic β-cell mass was measured at postnatal day 0 (P0) and 30 (P30). For *ex vivo* experiments Wild-type (WT) and ERβ-/- neonates as well as adult male and female mice were used. For *in vitro*, single islets cells were cultured for 48 h in the presence of 10 μmol/L BrdU, and vehicle, BPA (1, 10, 100 nM) or the specific ERβ agonist WAY200070 (1, 10, 100 nM). β-cell proliferation rate was quantified as the percentage of BrdU-positive pancreatic β-cells. *In vivo* exposure to BPA during pregnancy promoted an increment of pancreatic β-cell mass and proliferation in WT mice at P30 which was absent in ERβ -/- mice. In order to explore if these changes were related to a direct action of BPA on pancreatic β-cell division we performed a series of *ex vivo* experiments. Augmented β-cell proliferation rate was observed in BPA-exposed β-cells isolated from both adult male and female WT animals in comparison to controls. The increment was significant at all BPA doses tested. The effect was imitated by the selective ERβ agonist, WAY200070, and was abolished in cells from ERβ-/- mice. We also explored the effects of BPA in pancreatic β-cells from neonates and found an increment in BPA-exposed cells compared to controls, although the difference was only significant at the dose of 1 nM. A similar effect was observed in neonate cells treated with WAY200070 (10 nM). The effects on β-cell replication were abolished in cells from ERβ-/- neonate mice treated either with BPA or WAY200070. Our findings suggest that BPA modulate pancreatic β-cell growth and mass in an ERβ-dependent manner. This could have important implications for metabolic programming of T2DM. Ministerio de Economía y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER) grants BPU2017-86579-R (AN) and BFU2016-77125-R (IQ); Generalitat Valenciana PROMETEO II/2015/016 (AN). CIBERDEM is an initiative of the Instituto de Salud Carlos III.

Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

Characterising the Metabolism, Glucuronidation and Sulfation of C11-oxy C_{19} Steroids

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SAT-742

The metabolism of 11β-hydroxyandrostenedione (11OHA4), a major adrenal C_{19} steroid, was first characterised in our *in vitro* prostate models showing that 11OHA4, catalysed by 11βHSDs, 17βHSDs and 5α-reductases, yields potent androgens, 11keto-testosterone (11KT) and 11keto-dihydrotestosterone (11KDHT) in the 11OHA4-pathway [1]. Findings have since led to the analysis of C11-oxy steroids in PCOS, CAH and 21OHD. However, the only circulating C11-oxy steroids included to date have been 11OHA4, 11keto-androstenedione (11KA4), 11β-hydroxytestosterone (11OHT) and 11KT, with 11KT reported as the only potent androgen produced from 11OHA4. We have identified higher levels of 11KDHT compared to 11KT in prostate cancer tissue and benign prostatic hyperplasia tissue and serum, with data suggesting impeded glucuronidation of the C11-oxy androgens [2,3]. The assessment of 11KDHT and the inactivation/conjugation of the C11-oxy steroids in clinical conditions is therefore crucial.

We investigated the metabolism of testosterone, 11KT, 11OHT, dihydrotestosterone, 11KDHT and 11OHDHT in JEG-3 placenta choriocarcinoma, MCF-7 BUS and T-47D breast cancer cells, focusing on glucuronidation and sulfation. Steroids were assayed at 1 μM and metabolites were quantified using UPC^2-MS/MS. Conjugated steroids were not detected in JEG-3 cells with DHT (0.6 μM remaining) metabolised to 5α-androstane-3α,17β-diol and androsterone (AST), and 11KDHT (0.9 μM remaining) to 11OHAST and 11KAST. 11OHA4 was converted to 11KA4 (12%) and 11KT (2.5%); and 11KT to 11KDHT (14%). In MCF-7 BUS cells, DHT was significantly glucuronidated, whereas 11KDHT was not. 11KAST was the only steroid in the MCF-7 BUS and T-47D cells that was significantly sulfated ($p<0.05$). In parallel we investigated sulfation in the LNCaP prostate model. Comparing sulfated to glucuronidated levels, only DHT was sulfated, 26%. Analysis showed that C_{19} steroids were significantly conjugated (glucuronidated + sulfated) compared to the C11-oxy C_{19} steroids.

As there exists an intricate interplay between steroid production and inactivation, impacting pre- and post-receptor activation, efficient conjugation would limit adverse downstream effects. Our data demonstrates the production and impeded conjugation of active C11-oxy C_{19} steroids, allowing the prolonged presence of androgenic steroids in the cellular microenvironment. Identified for the first time is the 11OHA4-pathway in placenta and breast cancer cells, and the sulfation of 11KAST. Characterising steroidogenic pathways in *in vitro* models paves the direction for *in vivo* studies associated with characterising clinical disorders and disease, which the C11-oxy C_{19} steroids and their intermediates, including inactivated and conjugated end-products, have highlighted.

[1] Bloem, *et al.* JSBMB 2015, 153; [2] Du Toit & Swart. MCE 2018, 461; [3] Du Toit & Swart, JSBMB 2020, 105497.

Bone and Mineral Metabolism

PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS

Dry Cough as Only Sign of a Parathyroid Adenoma Producer of PTH

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