alterations in ACTH precursors and key enzymes controlling ACTH maturation and secretion in a mouse model of sepsis-induced critical illness.
Methods
C57Bl/6 mice were randomly allocated to a healthy control group or to 4 critically ill groups sacrificed after increasing illness duration (30 hours (H), 3 days (D), 5D or 7D). Critical illness was induced by sepsis brought about by cecal-ligation and puncture followed by fluid-resuscitation and antibiotics treatment. The study was continued until 15 surviving animals per time cohort were reached (n=120). We quantified pituitary pro-opiomelanocortin (POMC) gene/protein expression and POMC plasma concentrations, pituitary POMC intracellular trafficking and cleavage via intracellular POMC sorting/trafficking receptor Carboxypeptidase E (CPE) and prohormone convertase 1 (PC1/3) gene/protein expression. Gene expression of Annexin A1, an inhibitor of mature ACTH secretion, was quantified as marker of GR-mediated CORT-induced feedback inhibition at corticotroph level.
Results
Plasma CORT concentrations were median 3-fold increased during critical illness ($p<0.001$ for all time cohorts) in the face of normal (for 30H, 3D and 5D cohorts) to low (7D time cohort; $p=0.01$) plasma ACTH concentrations. Plasma POMC concentrations were higher in critically ill than in control mice ($p=0.05$). POMC gene expression (but not protein, $P=0.8$) was a median 55% higher in critically ill mice than in controls ($p<0.05$ for all time cohorts). In contrast, pituitary mature ACTH protein concentration was median 61% lower in critically ill than in control mice ($p<0.01$). CPE gene expression was only increased in 30H time cohort ($p<0.001$). PC1/3 gene and protein expression were positively correlated (R^2 0.1; $p=0.001$) and were reduced (by 37% and 43%, respectively) during the entire course of critical illness ($p<0.01$). Annexin A1 gene expression was increased during critical illness ($p<0.05$ for all time cohorts).
Conclusion
Suppressed CRH or AVP signaling and GR-mediated action within corticotrophs explained lack of elevated plasma ACTH in critical illness, as indicated by impaired POMC processing and ACTH maturation. However, increased POMC gene expression suggests ongoing corticotroph activation, the driver of which needs to be identified.
1. Teblick A *et al*. Nat Rev Endocrinol 2019

Adrenal

ADRENAL - TUMORS

Epidemiology of Adrenal Tumors: A Population Based Study of 1287 Patients

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Background: Adrenal tumors are reported in 5% of adults, with malignancy rates in 1–12%, and rates of overt hormonal excess in 1–15 %. However, most estimates originate from convenience samples. Our objective was to determine the incidence, prevalence and clinical presentation of adrenal tumors in a population-based setting.
Methods: We used a centralized epidemiologic database to identify patients diagnosed with adrenal tumors in a local community 1995 to 2017. The database is a unique medical records linkage system that allows access to hospital and community medical records for local residents (population 137,000). We calculated incidence rates (IR) as the number of new patients diagnosed while living in the study area, and prevalence as the number of patients living in the study area on Dec 31 2017. IR and prevalence were sex- and age-adjusted to the 2010 US Census population.
Results: Of 1,287 patients diagnosed with adrenal tumor, the median age of diagnosis was 62 years (IQR 52–72), 713 (55%) were women, and 13 (1%) were younger than 18 years at diagnosis. IR was highest in patients >65 YO, followed by patients 40–64 YO, 18–39 YO and <18 YO (142 vs 66 vs 9 vs 2 per 100,000 persons years). IR per 100,000 increased from 4.4 (CI95% 0.3–8.6) in 1995 to 47.8 (CI95% 36.9–58.7) in 2017. Overall prevalence in the population was 0.53% in 2017, ranging from 0.01% among 0–17 YO to 1.9% among +65 YO.
Malignant adrenal mass was diagnosed in 8.7% patients (4 patients with adrenal cortical carcinoma (0.3%) and 108 (8.4%) patients with other malignant mass). Pheochromocytoma was diagnosed in 11 (1.1%) patients and benign adrenal mass was diagnosed in 1,175 (90.2%) patients (1,076 (83.6%) with adrenal adenoma and 85 (6.6%) with other benign mass). Median tumor size was 15 mm (range 5–255), and 184 (14%) of patients had bilateral tumors. Only 255 (20%) patients had dexamethasone suppression test, 93 (36%) with cortisol>1.8 mcg/dl. Of 1,076 adrenal adenomas, 53 (4.9%) had overt hormone excess, 140 (13%) had nonfunctioning adrenal adenomas, and 88 (8.2%) had mild autonomous cortisol secretion. Hormonal work up for was incomplete in 795 (73.9%) adenomas. Patients discovered incidentally (1,050, 81.6%) had a lower rate of malignancy and hormone excess (5.3% vs 52% of patients with non-incidental discovery, $p<0.001$). Rate of malignancy was highest in children (67% vs 8% >18YO, $p<0.001$), bilateral tumors (16% vs 8% unilateral, $p<0.001$), tumors ≥4 cm (33% vs 7% in < 4 cm, $p<0.001$).
Conclusion: IR of adrenal tumors increased 10-fold since 1995, and was highest in patients >65 YO. 8.7% of tumors were malignant, with a majority represented by malignant adrenal tumors other than adrenal cortical carcinoma. The risk of malignancy was highest in non-incidental discovery, children, and tumors > 4 cm. Overt hormone excess was diagnosed in 4.5% of patients. The majority of patients with adrenal adenomas had a suboptimal work up for hormone excess.

Adrenal

ADRENAL - HYPERTENSION

Clinical Characterizations of Aldosterone- and Cortisol-Producing Adrenal Tumors in Primary Aldosteronism

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