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ADRENAL – CLINICAL RESEARCH STUDIES

Comparative Transcriptional Analysis of Patient Responders Versus Non-Responders to Glucocorticoid Treatment for Bronchopulmonary Dysplasia

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Bronchopulmonary Dysplasia (BPD) is a common heterogeneous lung disease that can result from preterm birth at less than 28-weeks gestation, prenatal and postnatal inflammatory insults, ventilator associated lung injury, and oxygen-related injury. Synthetic glucocorticoids (sGCs) are commonly used pre- and postnatally to treat inflammation and improve lung physiology. Clinical responses to sGC therapy for BPD vary in patients. We hypothesize that genetic background differences in transcriptional response to sGC therapy dictate the efficacy in infants with BPD. Identifying pathways and genes that mediate these differences will allow prospective determination of which infants would respond to sGC treatment.

26 preterm infants that received sGC treatment for BPD were identified. Respiratory Severity Score (RSS), an indication of BPD severity, was measured at diagnosis, 4 days, and 7 days post-sGC treatment. Patients were stratified into Responders versus Non-Responders by improvement in respiratory function after treatment. Changes in RSS were used to discriminate Responders (R >3 decrease in RSS) to treatment from Non-Responders (NR <3 decrease). 13 Responders and 13 Non-Responders were selected. They included 7 females and 19 males with an average gestational age of 24.3 weeks, and were 46% Caucasian, 31% African American, 19% Hispanic, and 4% other. 100μL of blood was collected before and after seven days of a dexamethasone treatment course.

To examine differences in transcription response between Responders (n = 13) and Non-Responders (n= 13), RNA was isolated and analyzed using the Clariom S Human Transcriptome Affymetrix array. 21,500 expressed genes were profiled. **Results:** were imported into the Transcriptome Analysis Console (TAC) software, and genes with a significant difference (fold change >1.48 or < -1.48 and p-value <0.05) in Responders and Non-Responders were identified. Of those, 133 genes were upregulated and 74 downregulated. Ingenuity Pathway Analysis (IPA) was used to identify signaling pathways and disease processes that were uniquely altered in Responders versus Non-Responders. Non-Responders showed significant activation of neuroinflammatory signaling pathways, degranulation pathways, and lymphocyte activation disease pathways. Target genes in the top dysregulated pathways were evaluated using quantitative Polymerase Chain Reaction (qPCR). Expression changes in Matrix Metalloproteinase-25, Interleukin-12 Receptor beta, and Microsomal Glutathione Transferase-1, key mediators of inflammation, were validated in independent studies using qPCR. While response to systemic glucocorticoids in neonates with BPD is variable, these studies identified pathways that are altered in Responders versus Non-Responders and are a step towards developing pre-screening tools to stratify infants for response to sGC BPD therapy.

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Concomitant Pheochromocytoma and Primary Aldosteronism: A Case Series and Literature Review

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Objective: The detection and management of concomitant pheochromocytoma (PHEO) and primary aldosteronism (PA) is not well understood. Our objectives were to investigate varying presentations and outcomes of cases with coexisting PHEO and PA to provide an approach to its diagnosis and management. **Design:** Retrospective case series from 2000–2020 at a single institution tertiary center; additional review of previously known cases before 2000 and from the medical literature. **Patients and Measurements:** Adult patients with concomitant PHEO and PA. Clinical, biochemical, radiologic, and histologic parameters were reviewed. **Results:** Fifteen patients (53% men, median age 53 years) were diagnosed with concomitant PHEO and PA. The majority presented with hypertension (13, 87%) and hypokalemia (13, 87%), but only 6 (40%) presented with symptoms suggestive of catecholamine excess. All patients with preoperative work-up for catecholamine excess (14, 93%) were found to have elevated plasma or urinary metanephrines/catecholamines above the upper limit of normal. Adrenal vein sampling (AVS) was performed in 9 (60%) patients, where 5 (56%) were diagnosed with bilateral PA, and 4 (44%) with unilateral PA. All patients underwent either unilateral (12, 80%) or bilateral (3, 20%) adrenalectomy to treat their PHEO and/or PA. Postoperative catecholamines and/or catecholamine breakdown products normalized or improved in 13 (87%) patients and were not measured in 2. Recurrence of PHEO was not observed. Six (40%) displayed persistent PA postoperatively, where 4 required long-term mineralocorticoid blockade. **Conclusions:** Concomitant PHEO and PA is a rare but likely underreported condition. Hypertension with or without hypokalemia should prompt evaluation for PA, while any indeterminate adrenal mass should be worked up for PHEO. Coexisting disease warrants consideration of AVS to determine the laterality of PA to ensure appropriate management.

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Confirmation of Feasibility of Selective Glucocorticoid Replacement Following Unilateral Adrenalectomy for Hypercortisolism and Primary Aldosteronism

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Background: Secondary adrenal insufficiency (AI) can develop following unilateral adrenalectomy (UA) foradrenal-dependent hypercortisolism (HC) and has been reported after UA for primaryaldosteronism (PA). An institutional study previously demonstrated that cosyntropin stimulationtesting on postoperative day 1 (POD1-CST) successfully identified patients who requiredglucocorticoid replacement (GR) following UA; 50% of HC patients required GR and no PApatients required GR. The aim of this study was to reevaluate the need for GR following UA forpatients with HC and PA in a larger cohort of patients. Methods We reviewed 108 patients from a prospectively maintained adrenal database who underwent UAfor HC (n=74), PA (n=22), and concurrent HC/PA (n=12) from 9/2014-10/2020. PA patientswithout preoperative evaluation for HC were excluded. Patients with 1mg dexamethasonesuppression test (DST) cortisol >1.8 (μg/dL) were defined as having mild HC, with ³5 defined asovert Cushing's Syndrome (CS). All patients underwent our institutional POD1-CST protocoland GR was initiated for patients with basal cortisol £5 or stimulated cortisol £14 (<18 prior to4/2017). **Results:** Overall, 51 (47%) patients had an abnormal POD1-CST and were discharged on GR (44 HC, 1PA, and 6 HC/PA). Two (2%) patients with CS had a normal POD1-CST but developed AIrequiring GR at 8 and 12 weeks post UA. Of the 74 patients with HC, 44 (59%) had an abnormalPOD1-CST and were discharged on GR, including 19/28 (68%) with CS and 25/46 (54%) withmild HC. Preoperative DST cortisol was higher in HC patients who required GR compared topatients with a normal POD1-CST (4.1 vs 3.6; p=0.007). Median cortisol levels for HC patientswith an abnormal POD1-CST vs those with a normal test were: basal: 3.8 vs 15.6 (p=0.027); 30-minute: 10.1 vs 20.1 (p=0.403); and 60-minute 11.4 vs 22.2 (p=0.260). Of the 22 PA patients, 19(86%) had a normal POD1-CST. Median cortisol levels for PA patients with an abnormal POD1-CST vs those with a normal test were: basal: 0.4 vs 12.1; 30-minute: 8.8 vs 24.6; and 60-minute:12.2 vs 28.9. Of the 3 (14%) PA patients with an abnormal POD1-CST, 1 was dischargedwith GR and began tapering after 2 weeks; the other 2 did not require GR and did not developAI. Of the 12 patients with combined PA/HC, 6 (50%) were discharged on GR based on POD1-CST. GR was required by 30 (59%) patients for <3 months and 82% for <12 months; 7/9 whorequired GR >12 months had CS. **Conclusions:** Using a standard protocol for POD1-CST in patients who underwent unilateral adrenalectomyfor HC, PA, or combined PA/HC, this study demonstrated that routine GR is not required in 32%of patients with CS and 46% of patients with mild HC. POD1-CST safely identifies patients whowill require GR with no immediate concern for adrenal insufficiency. These data also suggestthat routine evaluation for AI in postoperative PA patients is not needed if cortisol excess hasbeen excluded preoperatively.

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Cortisol Levels Is Associated With Left Ventricular Diastolic Dysfunction in Diabetic Patients

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Introduction: Diabetes mellitus (DM) is a major cause of cardiovascular disease including heart failure with preserved ejection fraction (HFpEF), which is characterized by left ventricular diastolic dysfunction (LVDD). It is reported that Cushing's syndrome is also associated with LVDD. The relationship between plasma cortisol concentration and LVDD, however, has not been investigated in patients with DM. **Methods:** In this study, 109 patients with DM and 104 patients with non-DM without overt heart failure were enrolled. Left ventricular function were assessed using echocardiography. The ratio of early diastolic velocity (E) from transmitral inflow to early diastolic velocity (e') of tissue Doppler at mitral annulus (E/e') was used as an index of diastolic function. Parameters of plasma cortisol concentration, glycemic control, lipid profile, treatment with anti-diabetic drugs and other clinical characteristics were evaluated, and their association with E/e' determined. Patients taking steroids, undergoing dialysis treatment and with overt heart failure were excluded. **Results:** Univariate analysis showed that E/e' was significantly correlated with age (p<0.001), duration of diabetes (p=0.039), systolic blood pressure (SBP) (p<0.001), eGFR (p=0.002), sodium glucose cotransporter 2 (SGLT2) inhibitor use (p<0.001) and cortisol (p=0.009) in patients with DM. Multivariate linear regression analysis showed that log E/e' was positively correlated with age (p=0.018), log SBP (p= 0.005), eGFR (p=0.015), cortisol (p=0.028) and that log E/e' was inversely with inhibitor use (p=0.018). There was no association between E/e' and cortisol in patients with non-DM. **Conclusions:** Cortisol may be important in the development of LVDD in patients with DM.

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Deliberate Compensated Vasoplegia - a Novel Pharmacological Regimen for Controlling Arterial Blood Pressure During Surgery for Pheochromocytoma

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Background: Intraoperative hemodynamic fluctuations are the most dreaded phenomenon associated with the treatment of pheochromocytoma. Preoperative alpha-adrenergic blockade protocols aimed at abating these fluctuations have achieved controversial results. No study to date has evaluated the use of intraoperative treatment protocols during surgery for pheochromocytoma. Deliberate compensated vasoplegia (DCV) is a novel pharmacological regimen developed at our institution intended to decrease