# Adrenal Disorders

## Adrenal Gland physiology

- Adrenal glands have cortex and medulla
- cortex has 3 layers
  - outer zona glomerulosa : secretes mineralocorticoids aldosterone
  - intermediate zona fasciculata : secretes cortisol
  - inner zona reticularis : secretes adrenal androgens
- the medulla is functionally related to the sympathetic nervous system and secretes the catecholamines epinephrine and norepinephrine in response to stress
- Cortisol is secreted in response to ACTH which is regulated by CRH and vasopressin AVP
- Renal juxtaglomerular cells secrete renin in response to a decrease in circulating volume, a reduction in renal perfusion pressure or both - Renin is the rate limiting enzyme that converts angiotensinogen synthesized by the liver to Angiotensin 1 - it is rapidly converted to Angiotensin 2 by ACE produced by the lungs - aldosterone production
- Aldosterone secretion is regulated by : Angiotensin 2 / plasma potassium concentration / plasma volume / ACTH
- Binding of aldosterone to the cytosol mineralocorticoid receptor leads to sodium absorption and potassium and hydrogen secretion by the renal tubules resulting in an increase in plasma volume and Na concentration
- cortisol function : increase catabolism and decrease anabolism / raise insulin levels / increase glycogen synthesis / stimulate osteoclasts and PTH but reduce calcium absorption / increase cardiac output and sodium retention / daytime fatigue / Nocturnal hyperarousal / Decreased short term memory / Decreased cognition
- Cortisol is normally secreted in a diurnal manner : The plasma concentration is highest in the early morning ( between 6:00-8:00 am) and lowest around midnight

## Adrenal Insufficiency

- Glucocorticoid insufficiency can be primary ( resulting from destruction or dysfunction of the adrenal cortex ) or secondary resulting from pituitary disorder of ACTH hyposecretion )
- secondary is much more common than primary
- Autoimmune destruction of the adrenal glands ( Addison disease ) is the most common cause of primary adrenal insufficiency affecting glucocorticoid and mineralocorticoid secretions
- patients with Addison disease have antiadrenal antibodies directed at 21 alpha hydroxylase CYP21A2

- other causes :
  - calcified adrenal glands
  - TB and HIV
  - Waterhouse Friderichsen syndrome : Hemorrhagic destruction of the adrenal glands
- Addison′ disease may be part of 2 distinct autoimmune polyglandular syndrome :
  - The triad of hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis characterizes type 1 polyglandular autoimmune syndrome called autoimmune polyendocrinopathy 1 APECED which usually manifests in childhood
  - type 2 polyglandular autoimmune syndrome called Schmidt syndrome : characterized by Addison disease, autoimmune thyroid disease ( Graves or Hashimoto ), insulin dependent diabetes mellitus and hypogonadism
- Clinical Manifestations
  - Primary : hyperpigmentation ( due to increased ACTH ) / Hypoaldosteronism ( hyponatremia, hyperkalemia, hypovolemia ) / salt craving / mild metabolic acidosis / azotemia / hypercalcemia
  - Secondary : no effect on pigmentation / decreased libido / impotence / diabetes insipidus / delayed puberty
  - Both : NVD / orthostatic hypotension / weight loss / anorexia / fatigue / lymphocytosis / hypoglycemia / normocytic anemia
- Diagnosis
  - In primary adrenal insufficiency plasma ACTH levels will be elevated whereas in secondary adrenal insufficiency plasma ACTH levels will be low or normal
  - low morning cortisol level
  - Gold standard test is insulin induced hypoglycemia or insulin tolerance test
  - ACTH stimulation test ( cosyntropin ) .. if below 18.5
  - Adrenal CT for Primary hypoadrenalism
  - Pituitary MRI for Secondary hypoadrenalism
- Long term treatment
  - Glucocorticoid Replacement : Hydrocortisone
  - Mineralocorticoid Replacement : Fludrocortisone

## 21 Hydroxylase Deficiency ( CYP21A2 )

- reduced cortisol and aldosterone synthesis
- results in reduced negative feedback and increased ACTH secretion and adrenal androgens are produced in excess
- has many forms and it is more common in jews

- Simple Virilizing Form
  - Females : clitoral enlargement, labial fusion, urogenital sinus development, sexual ambiguity at birth, inappropriate sex assignment ( at birth )
  - Males are phenotypically normal at birth
- Salt Wasting Form : aldosterone deficiency with hypotension
- Nonclassic Late Onset form : polycystic ovary syndrome PCOS / hirsutism / primary or secondary amenorrhea or oligomenorrhea / anovulatory infertility / Androgenic alopecia / acne

## Cushing Syndrome

- Cushing syndrome refers to any condition of endogenous glucocorticoid excess while Cushing disease refers to an ACTH secreting pituitary tumor leading to glucocorticoid excess
- may be caused by exogenous administration of ACTH or glucocorticoid or by endogenous overproduction of these hormones
- Endogenous Cushing's syndrome is either ACTH dependent or ACTH independent
- ACTH dependency accounts for 85% of patients and includes pituitary sources of ACTH ( Cushing disease ) and ectopic sources of ACTH like lung small cell carcinoma
- Symptoms :
  - Fat redistribution ( dorsocervical and supraclavicular fat pads ) aka buffalo hump
  - temporal wasting
  - centripetal obesity and weight gain
  - Menstrual irregularities
  - Thin skin and plethora
  - Moon face
  - Increased appetite
  - Sleep disturbances and Nocturnal hyperarousal
  - Hypertension
  - Hypercholesterolemia and hypertriglyceridemia
  - Altered mentation ( poor concentration, decreased memory, euphoria )
  - Diabetes mellitus and glucose intolerance
  - Violaceous Striae ( dark red or purple )
  - Hirsutism and Acnes
  - Proximal muscle weakness
  - Psychological disturbances ( emotional lability, depression, mania, psychosis )
  - Decreased libido and erectile dysfunction

    - Osteoporosis and pathologic fractures with Easy bruisability
    - aseptic necrosis mainly of femoral head
    - Poor wound healing
    - Virilization
    - Edema
    - Increased infections and Cataracts
- Pseudocushing Syndrome
    - Depression
    - Obesity
    - Physical stress
    - Malnutrition and Eating disorders
    - PCOS
    - Uncontrolled diabetes
    - Obstructive sleep apnea
    - Chronic alcoholism
- Diagnosis :
    - collecting urine for 24 hours and measuring the urinary free cortisol UFC .. the initial UFC level is greater than 50 µg/24 hour
    - low dose Dexamethasone suppression test : 1 mg is given orally at 11:00 pm or midnight, and plasma cortisol is measured the following morning at 8:00 am .. A morning plasma cortisol level greater than 1.8 µg/dL suggests hypercortisolism
    - late night salivary cortisol

## Hyperaldosteronism

- Causes : aldosterone producing adenoma, bilateral adrenal hyperplasia and adrenal carcinoma
- Clinical presentation : Hypertension, hypokalemia, metabolic alkalosis, fatigue, muscle weakness, nocturia, lassitude and headaches
- A positive Trousseau or Chvostek sign may occur as a result of metabolic alkalosis
- Diagnosis :
    - Plasma renin activity PRA
    - plasma aldosterone concentration PAC
    - 24 hour aldosterone urine test
- Treatment : adequate salt intake, aldosterone producing adenoma is treated with surgery and bilateral adrenal hyperplasia is treated medically

## Adrenal Medullary Hyperfunction ( Pheochromocytoma )

- Norepinephrine is the major catecholamine produced by the adrenal medulla has predominantly alpha agonist actions, causing vasoconstriction
- Epinephrine acts primarily on the beta receptors causing peripheral vasodilation and increasing plasma glucose concentrations in response to hypoglycemia
- Hypofunction of the adrenal medulla has little physiologic effect whereas hypersecretion of catecholamines produces the clinical syndrome of pheochromocytoma
- pheochromocytomas can occur in any sympathetic ganglion in the body, more than 90% arise from the adrenal medulla
- Sipple syndrome is marked by medullary carcinoma of the thyroid, hyperparathyroidism and pheochromocytoma
- Pheochromocytomas are also associated with neurofibromatosis, cerebelloretinal hemangioblastoma ( von Hippel Lindau disease ) and tuberous sclerosis
- Clinical presentation
    - Hypertension not responsive to antihypertensives
    - Triad : headache / diaphoresis ( sweating ) / tachycardia
    - skin blanching, diarrhea, anxiety, nausea, fatigue, weight loss
    - labile blood pressure
    - abdominal and chest pain
- Diagnosis :
    - plasma free metanephrine and normetanephrine levels are the best tests for confirming or excluding pheochromocytoma
    - clonidine suppression test
    - adrenal CT
- Treatment : surgery

## Adrenal Incidentalomas and Adrenal Carcinoma

- Incidentalomas are uncommon in patients younger than 30 but increase in frequency with age and They occur equally in males and females
- Incidentalomas may represent myelolipomas, hamartomas, or granulomatous infiltrations of the adrenal glands
- Some incidentalomas may cause abnormal hormone secretion without obvious clinical

manifestations of a hormone excess state
    - the best example of this relates to Preclinical Cushing syndrome
- All patients with incidentally discovered adrenal masses should undergo appropriate endocrine screening tests:
    - 24 hour urinary catecholamine collection
    - Low dose DST
    - If history of HTN, check supine circulating PRA and aldosterone levels
    - DHEAS should be measured for androgens abnormalities
- In true incidentalomas, size appears to be predictive of malignancy : a lesion less than 4 cm in diameter is most unlikely to be malignant ( The majority of nonfunctioning lesions less than 4 cm can therefore be treated conservatively and patients followed up with annual imaging )
- Even incidentalomas greater than 6 cm are more likely to be benign than malignant but because of an increased risk of malignancy ( about 30% ) many centers recommend removal of tumors greater than 6 cm in diameter
- Primary Adrenal Carcinoma
    - rare and more in women mainly 40-50 years of age
    - majority are functional ( cortisol is the most common / then with androgens / then androgens )
    - abdominal pain, weight loss, anorexia, and fever occur in 25% of cases
    - An abdominal mass may be palpable.
    - Radiotherapy is ineffective as are chemotherapeutics
    - poor prognosis