Disorders of the Adrenal Glands

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Cortex

• Steroid hormones cortisol, aldosterone and androgens are synthesized

• Derived from cholesterol

• Three histologic zones – glomerulosa (aldosterone), fasiculata and reticularis
Cortisol

- Secretion is regulated by hypothalamus (CRH) and the pituitary (ACTH)
- Exerts effects on intermediary metabolism through variety of cells and tissues
- Stimulates hepatic gluconeogenesis and glycogen synthesis
Cortisol

- Inhibits protein synthesis, increases protein catabolism and fat lipolysis
- Inhibits peripheral uptake of glucose in most tissues (liver, brain and RBCs)
- Promote collagen loss and impairment of wound healing (inhibit fibroblast activity)
Cortisol

• Inhibit bone formation

• Inhibit numerous anti-inflammatory actions

• Critical for cardiovascular stability
Androgens

- Synthesized primarily in zona reticularis – DHEA
- Peripheral conversion to testosterone and dihydrotestosterone
- Account for less than 5% of normal male testosterone production
Aldosterone

• Regulation of ECF volume

• Regulation of Na and K balance

• Release is stimulated by renin through renin-angiotensin-aldosterone pathway
Adrenal Medulla

- Derived from neural crest cells
- Principal site for catecholamine synthesis
- Only site for the enzyme PNMT
- Converts NE to EPI
Disorders of the Adrenal Cortex
Primary Hyperaldosteronism

- Conn syndrome
- Responsible for HTN in 8 to 12% of pts
- Characterized by early onset, difficult to control, associated with hypokalemia
- As many as 60% of patients will be normokalemic at time of diagnosis
Investigative Studies

• Initial biochemical evaluation should consist of measurement of plasma aldosterone concentration and plasma renin activity

• PAC:PRA > 25 to 30 with a suppressed PRA (< 0.2 - 0.5) and a PAC > 15

• Confirmed by suppression testing with either oral salt loading or IV saline administration
Diagnosis

• Once the diagnosis is confirmed biochemically – must identify cause or determine subtype

• Historically aldosteronomas have accounted for 60% followed by bilateral cortical hyperplasia

• Bilateral hyperplasia has become more common – 50 to 70%
Familial Hyperaldosteronism I

- Glucocorticoid-remediable hyperaldosteronism
- Autosomal dominant
- Chimeric gene that results from fusion of two components
- Aldosterone synthesis dependent on ACTH
- Suppressed by exogenous glucocorticoid administration
Imaging

• Initial step is to perform cross-sectional imaging to look for adenoma

• Thin section imaging with CT scan is the preferred modality

• MRI
Adrenal Vein Sampling

Aldosterone-to-cortisol ratio at least 4 to 5x greater on one side = unilateral source of increased aldosterone production
Management

• Lap adrenalectomy for aldosteronoma

• Pre-op control of HTN

• Correction of hypokalemia
Management

- Medical for idiopathic hyperaldosteronism
- Dietary sodium restriction
- Oral potassium supplementation
- bp control – spironolactone
Cushing Syndrome

- Uncommon – 1 to 10 per million
- *ACTH*-secreting pituitary and ectopic tumors or cortisol producing adrenal tumors
- Small cell lung CA = most common ectopic source
- Also seen with thymic, carcinoid and MCT tumors
Clinical Evaluation
Cushing Syndrome

- Obesity = most consistent feature
- Central pattern – face, trunk, neck and abdomen
- Buffalo hump
- Skin changes – easy bruising, fragility and striae
Diagnosis

• Determine whether state of increased cortisol production exists

• Determine whether cause is ACTH dependent (pituitary and ectopic) or independent (adrenal)

• Locate the source
Investigative Studies
The initial diagnostic test should be measurement of urinary free cortisol and an overnight dexamethasone suppression test.

Urinary free cortisol levels are elevated in 90% of pts with Cushings.

FP with meds, obesity, serious illness or depression.

Can miss mild degree of hypercortisolism.
Suppression Testing

- Dexamethasone is a potent glucocorticoid that suppresses adrenal production of corticosteroids in normal persons but not in those with Cushings

- Low-dose dexamethasone suppression

- Loss of normal diurnal variation
After diagnosis is established – plasma ACTH is measured

ACTH normal to moderately elevated = pituitary Cushing

Ectopic ACTH = levels are usually higher

Adrenocortical tumor = levels suppressed
ACTH-dependent

- Pituitary or ectopic
- High-dose dexamethasone suppression
- Suppresses ACTH from most pituitary but not ectopic sources
Localization

- Radiographic
- CT – for suspected adrenal source
- MRI – for suspected pituitary source
- Measurement of inferior petrosal sinus ACTH levels = the most direct method of differentiating pituitary from non-pituitary causes
Adrenocortical Carcinoma
ACCA

- Rare
- 0.5 to 2 per million
- Bimodal age distribution (childhood and 4\textsuperscript{th} to 5\textsuperscript{th} decades)
- Large (6 to 8 cm) at presentation
- Advanced disease
- 60\% are hyperfunctioning
Management

- ACCA is an aggressive tumor that may spread locally to regional LNs, adjacent organs and distant sites (liver, lungs and bones)

- Complete surgical resection offers the only chance for cure and is the best predictor of clinical outcome
Adrenal Insufficiency
Clinical Evaluation

• Primary or secondary

• Chronic AI = Addison Disease

• Characterized by weakness, chronic fatigue, anorexia, abdominal pain, nausea and diarrhea

• Sx of primary AI are usually more severe than secondary
Presentation

- Acute adrenal crisis can be precipitated by the stress surgery, trauma, infection or dehydration

- Can result in vascular collapse with hypotension, shock and death

- In pts with unexplained CV collapse in whom the Dx is suspected should be treated empirically with corticosteroids
Diagnosis

• Confirmed by measurement of plasma cortisol and ACTH levels

• In primary AI, AM cortisol levels are typically low and ACTH levels high

• ACTH stimulation test
Management

• Exogenously administered glucocorticoids

• Acute adrenal crisis – hydrocortisone 100 mg every 8 hours

• Oral replacement therapy with either hydrocortisone or prednisone for chronic AI
Disorders of the Adrenal Medulla
Pheochromocytoma

- Catecholamine-producing tumors
- Arise from chromaffin tissue
- 85 to 90% arise in the adrenal gland
- Extra-adrenal do occur
- Peak in the 4th to 5th decade of life
Pheochromocytoma

- Affect males and females equally
- Present in 0.1 to 0.5% of HTN patients
- Clinically silent pheos can arise in 10% of patients with incidentalomas
- Rule of 10s
Rule of 10s

- Extra-adrenal
- Bilateral
- Children
- Familial
- Malignant
Extra-adrenal

- Paragangliomas
- Lack the enzyme PNMT
- Can secrete NE but not EPI
Clinical Evaluation

• Clinical features are related to the effects of increased secretion of NE and EPI

• HTN is most consistent feature – either paroxysmal or sustained

• Paroxysmal can be severe and associated with spells
Spells

- Pounding in the chest
- Tachycardia
- Headache
- Anxiety
- Pallor

Related to catecholamine surge - < 15 min
Symptoms

- Increased temp, flushing, sweating
- Feeling of marked anxiety and impending sense of doom
- Attacks can occur spontaneously or triggered by postural changes, vigorous exercise, sex, drugs or anesthetics
Investigative Studies
Diagnosis

• Demonstrate elevated levels of either catecholamines and metabolites or of fractionated metanephrines in plasma

• Urinary VMA is the least specific test – high frequency of FP

• Plasma fractionated metanephrine level is the preferred initial screening test
Diagnosis

• Some prefer measurement of 24-hr urinary catecholamine and metanephrine levels

• Abnormal plasma metanephrine and NE levels should be confirmed by measurement of urinary catecholamine and metanephrine concentrations

• Direct measurement of plasma catecholamine levels during HTN crisis
Imaging

- Only 2 to 3% of pheos are found outside the abdomen
- Localization should begin with abdominal CT or MRI
- Appear bright on T-2 weighted MRI
- MIBG
MIBG

- Selectively accumulates in chromaffin tissues – does so more rapidly in pheos than in normal adrenal medullary tissue
- Overall sensitivity of 77 to 90%
- Specificity of 96 to 100%
- Most useful for localizing extra-adrenal pheos
Pre-op

- Pharmacological prep prior to op targeted to prevent intraop HTN crisis
- Alpha blockade with phenoxybenzamine is initiated until orthostatis is achieved
- Volume load with IV hydration to fill expanded extravascular space
- Beta blockade may also be required
Beta blockade should never be initiated until alpha blockade has first been achieved

Unopposed alpha receptor stimulation can trigger a HTN crisis
Management

• Intraop arterial line

• Higher vascular – lap approach is feasible

• Intraop bp exacerbation can be managed with esmolol or nitroprusside

• Should monitor for 24 to 48 hours – both hemodynamics and glucose
MEN IIA

- Parathyroid hyperplasia
- MCT
- Pheo
MEN IIB

- Marfanoid body habitus
- Multiple mucosal neuromas
- MCT
- Pheo
Incidentaloma

- Most commonly encountered adrenal lesion
- Occur in 1 to 5% of patients undergoing CT scans for other reasons
- Secondary to increased frequency of cross-sectional imaging
Clinical Evaluation
Incidentaloma

- Most are clinically silent
- Do not secrete excess adrenal hormones
- Do not cause pain
Differential Diagnosis

• Functioning adrenal tumors

• Primary or metastatic adrenal malignancy

• Nonfunctioning lesions
Incidentaloma

- Nonfunctioning cortical adenoma = most common
- Accounts for 60% of cases
- Hyperfunctioning tumors include cortisol-producing adenomas (subclinical) and pheos
Bilateral

- Adrenal cortical hyperplasia
- Bilateral pheos
- Metastases
- Lymphomas
- Myelolipomas
- Infection (tb)
Investigative Studies
Work-up

- Goal
- Determine if lesion is hypersecretory
- Determine likelihood of malignancy
Work-up

- Overnight dexamethasone suppression
- Measure plasma concentration of fractionated metanephrines or urinary catecholamines and metanephrines
- Measure plasma aldosterone and renin levels if patient is HTN or hypokalemic
Imaging

- Assess imaging features
- Size
- < 4 cm unlikely to be malignant without a known malignancy
- Benign lesions are smooth and homogeneous
- Malignant lesions have irregular contours and areas of inhomogeneity
Biopsy

- Needle biopsy is rarely indicated
- Does not differentiate between benign and malignant adrenal cortical tumors
- Associated with not insignificant complications
Management

- Most recommend removing nonfunctioning adrenal masses larger than 5 cm
- Observe masses smaller than 3 cm
- Management of masses 4 to 5 cm should be individualized
- If resection is not indicated - repeat imaging at 4 to 6 months and repeat imaging and biochemical testing at 1 year
Adrenal Metastases

- Occur most commonly in the setting of more widespread metastatic disease

- Renal cell CA, lung CA and melanoma = most commonly met to adrenal

- Imaging characteristics include larger size (>3cm), higher attenuation on CT and no signal loss on MR chemical-shifted imaging
Adrenalectomy

- Any adrenal lesion that is hyperfunctioning
- Any adrenal lesion that is suspected of being malignant or possibly malignant on the basis of size or other imaging criteria
- Adrenal mets should only be resected if they are solitary and appear in the absence of extra-adrenal met disease
Adrenal mass is incidentally discovered on diagnostic imaging

Carry out biochemical evaluation:
- Measure plasma concentrations of fractionated metanephrines or urinary levels of catecholamines and metanephrines.
- Perform dexamethasone suppression test.
- If the patient is hypertensive or hypokalemic, measure plasma concentrations of aldosterone and renin.

Carry out radiographic assessment, reviewing images for lesion size, attenuation, and homogeneity. If CT cannot determine the nature and characteristics of the lesion, perform MRI.

Lesion is nonfunctioning, < 4 cm, and benign appearing
- Observe patient. Repeat imaging at 4 and 12 mo. Repeat biochemical evaluation at 12 mo.

Lesion is functioning
- Perform adrenalectomy.

Lesion is > 4–5 cm or has atypical appearance