THE ADRENAL GLAND: WHAT DO WE NEED TO KNOW?

Rahfa K. Zerikly MD
OBJECTIVES

- Overview of adrenal pathology
- Labs choices and rationale
- Expanding on Adrenal insufficiency, diagnosis and management
- Exogenous Steroid effect on Adrenals and management
- Adrenal mass, case detection, diagnostic approach
Endocrinologist known among their colleagues as physicians who order blood and urine!
“MEASURE SOMETHING”
“Testing for the sake of testing is both foolish and expensive”
## Laboratory Testing

- What are you measuring?
- Why are you measuring it?
- When are you measuring it?
- What are the advantages and pitfalls of the assay?
Understanding the biochemical basis of an endocrine disorder could eventually lead to its proper diagnosis.
• Not yet a general consensus about what defines “normal”, “optimal”, “abnormal” for any given hormone

• These definitions are continuously undergoing revision
Another Concept

Two simple rules to determine whether low or high hormone concentrations are Physiologic or Pathologic

“If it is low, stimulate it; If it is high, suppress it”
Understanding the physiological basis of an Endocrine problem is equally critical
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis
Regulation of aldosterone secretion

- Renal arterial pressure
- β-adrenergic action
- Prostaglandins

Liver → Angiotensinogen → Angiotensin I → Angiotensin II

Renin → Kidneys → Aldosterone

Aldosterone → Kidneys → Extracellular volume

Renal arterial pressure

Na⁺ (+ water) retention

K⁺ excretion

ECF [K⁺]
A Regulation of cortisol secretion

- Stressors (hypoglycaemia, hypotension, fever, trauma, surgery)
  - Diurnal rhythm
  - Hypothalamus
    - CRH
      - ADH, Cytokines
      - Pituitary
        - ACTH
          - Adrenals
            - Cortisol

Cardiovascular system:
- Myocardial contractility
- Cardiac output
- Catecholamine pressor effect

Metabolism:
- Gluconeogenesis
- Glycogenolysis
- Proteolysis
- Lipolysis
Stress Response

• Acute psychological stress raises cortisol

• Chronic anxiety states and underlying psychotic illness: normal secretion rate

• Depression: Higher circulating cortisol secretion
Circadian Rhythm

- ACTH secreted in pulsatile fashion with circadian rhythm
- Wakening: Highest. Increased ACTH pulse amplitude between 5-9 am
- Decline throughout the day
- Evening: Nadir. Reduction in pulse frequency between 6 pm - midnight
Circadian Rhythm

- Dependent on both:
  - Day-night
  - Sleep-wake patterns
- Disrupted by: Alternating day-night shift work & long distance travel across time zones
- Can take up to 2 weeks to reset to an altered day-night cycle
Should be taken into account when measuring plasma “total Cortisol”

- >90%: Bound
- Predominantly: CBG
- Increased:
  - Estrogen; OCP, pregnancy (2-3 fold)
  - Chronic active hepatalogy
- Decreased:
  - Glucocorticloid
  - Cirrhosis
  - Nephrosis
  - Hyperthyroidism
Other Factors To Be Considered

- Hyperthyroidism: Increase metabolism & clearance
- Hypothyroidism: Opposite
- Rifampin & Phenytoin: Increase clearance
- Renal disease: Impaired clearance
Case Study

- 62 y/o woman
- 1 week history of increasing fatigue, weakness, postural lightheadedness and lack of appetite
- 2 days history of N, occ V, bilateral flank pain
- Lost 10 pounds
- VS
  - BP 92/56, orthostatic change of 10 mm hg, BMI 32.4
Case Study

- Skin normal, minimal darkening of the palmar creases
- 3 mo earlier, presented with DVT/PE
- Initially treated with Heparin and now taking Warfarin
Abdominal CT
What Is The Next Step

- What labs needed?
- Therapy?
Biochemical Evaluation

- Demonstrating inappropriately low Cortisol secretion
- Determining whether Cortisol deficiency is dependent on or independent of ACTH deficiency
- Evaluating Mineralcorticoid secretion in patients without ACTH deficiency
- Seeking a treatable cause
RANDOM CORTISOL IS NOT USEFULL
Adrenal Insufficiency

- 8 AM Cortisol <3 mcg/dL is strongly suggestive of AI
- 8 AM Cortisol >15 mcg/dL predicts normal serum Cortisol response to ITT or ACTH Stim in virtually all patients
- 8 AM Cortisol >18 mcg/dL even more assuring
- Obviates more sophisticated and expensive testing
What Is The Expected Lab Profile

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Cortisol (8 AM)</th>
<th>ACTH (8 AM)</th>
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<tbody>
<tr>
<td>A</td>
<td>129</td>
<td>5.2</td>
<td>0.9</td>
<td>600</td>
</tr>
<tr>
<td>B</td>
<td>144</td>
<td>3.4</td>
<td>44</td>
<td>&lt;10</td>
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<tr>
<td>C</td>
<td>140</td>
<td>4.0</td>
<td>14</td>
<td>20</td>
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<tr>
<td>D</td>
<td>129</td>
<td>4.8</td>
<td>0.9</td>
<td>&lt;10</td>
</tr>
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<td>E</td>
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<td>3.4</td>
<td>44</td>
<td>600</td>
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</tbody>
</table>
If equivocal results in 8 AM Cortisol, need Stimulation Test
Stimulation Test

- Gold Standard: Insulin Tolerance Test (ITT)
- Induce symptomatic hypoglycemia (severe stressful situation) to stimulate HPA axis
- Risks: Elderly, multiple co-morbidities, CVD, seizures
- Physician must be present
- Useful to Dx acute and chronic AI & GHD
Insulin Tolerance Test

Normal

Hypopituitary

Plasma Glucose (mmol/L)

Plasma Cortisol (nmol/L)

Serum GH (µg/L)

Time (minutes)

Range of normal response
ACTH (1-24 cosyntropin) Stim

- Only parameter used is Peak Cortisol (18 ug/dL)
- 250 mcg (reaches serum ACTH levels much higher than those encountered in stressful situations: Supra-physiological stimulation level)
- 1 mcg found to reach serum ACTH comparable to those in stressful situation

Alia et al (Clin Endo 2006)
Expected Cortisol Peak in Relation to Dosage

- Using 1 mcg ACTH, 30-min response did not differ from that to 250 mcg
  - However, 60-min response to 1 mcg significantly lower

- If using 250 mcg ACTH: Use the 30 min or the 60 minutes peak value

- If Using 1 mcg ACTH: Use the 30 minutes peak value

• Dickstein G et al. JCEM (1991)
Expected Cortisol Peak in Relation to Time

- Despite significantly different baseline levels, 30-min Cortisol levels not different (618 +/- 50 vs. 590 +/- 52 nmol/L) in AM vs. PM

- Afternoon peak found significantly higher than morning levels at 5 min and 15 min

- Difference in response no longer notable at 30 min

• Dickstein G et al. JCEM (1991)
Conclusion

• The 30-min Cortisol response to ACTH is constant, unrelated to basal Cortisol level or time of day

• Data show that there is probably no diurnal variation in the response of the adrenal to ACTH
LDT Advantages

- Higher Sensitivity
- Identify mild HPA suppression:
  - Low dose ACTH test enabled to differentiate a subgroup of patients on long-term steroid treatment who responded normally to the regular 250 mcg test, but had a reduced response to 1 mcg (Dorsey et al, Ann Allergy Asthma Immunol 2006)
- Identify partial primary adrenal insufficiency
LDT Limitations

- Recent onset secondary/central pituitary insufficiency in which their response to ACTH can still be normal until adrenals atrophy

- How long this response can last?
  - Controversial
  - Suggested 6-12 weeks

- Shared with the HDT
Source of Error

- Failure to inform the physician of other medications that may interfere with the diagnostic tests, the hormonal assays, or both
- Obtain Accurate, detailed medications history including over the counter medications
Which does not cross-react?

A. Dexamethasone  
B. Hydrocortisone  
C. Methyl-prednisolone  
D. Prednisone

ALL BUT DEXAMETHASONE
Pitfalls

- Presumes that CBG concentration is normal
- Low CBG (critical illness, cirrhosis, or nephrotic syndrome) result in a lower than expected Cortisol value
- Conversely, high CBG (oral estrogen use) increases serum cortisol concentrations
- If missed lead to incorrect diagnosis
- Salivary or Serum free Cortisol suggested as alternatives
  - Not widely available
  - Criteria for response not been developed, Not standardized
  - Suggested approaches (Arafah: Review JCEM 2006)
Etiology of 1° Adrenal Insufficiency

- Autoimmune adrenalitis
- Infectious (TB, CMV, Fungi, HIV...)
- Infiltrative (Amyloid, Hemochromatosis)
- Hemorrhagic [eg. antiphospholipid syndrome]
- Metastatic cancer
- Medications (Etomidate, Azole, metyrapone, mitotane, Mifepristone)
- Congenital
When Primary AI is Diagnosed...

- Abdominal CT indicated as first step

- Autoimmune? Consider polyglandular autoimmune syndrome
  - Check Ca, Pho, Glucose, TSH, Testosterone in men, FSH in hypogonadal men and women
Central 2° Adrenal Insufficiency

- Most common cause: Supra-physiological Glucoroticoid therapy
- Less common: Pituitary hypothalamus lesion
  - Tumor, Infiltrative lesions, Mets
  - History Radiation Tx (can take up to 10 yrs)
  - Lymphocytic hypophysitis (isolated Cortisol deficiency)
  - Megestrol (suppresses HPA axis, binds to glucorticoid receptors): AI after withdrawal
- In the absence of history of exogenous steroid use
  - Pituitary MRI indicated
Central 2° Adrenal Insufficiency

- Differs from primary
- Aldosterone secretion normal
- No salt craving or hyperkalemia
- Mineralcorticoid Tx not indicated
- ACTH not elevated
- No hyperpigmentation
- Signs: Subtle, non-specific
<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td><strong>Symptoms</strong></td>
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<td>Weakness, tiredness, fatigue</td>
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<td>Nausea</td>
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<td>Vomiting</td>
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<td>Constipation</td>
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<td>Abdominal pain</td>
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<td>Diarrhea</td>
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<td>Salt craving</td>
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<td>Eosinophilia</td>
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</table>
AI Progression

- Loss of more than 90% of function results in Sxs
- Rapid destruction: Acute crisis
- Gradual destruction
  - Initial phase: Basal steroid secretion - normal
  - Secretion does not increase in response to stress (surgery, trauma, infection...) leading to acute crisis
### TABLE 15-19

**Clinical and Laboratory Features of an Adrenal Crisis**

- Dehydration, hypotension, or shock out of proportion to severity of current illness
- Nausea and vomiting with a history of weight loss and anorexia
- Abdominal pain, so-called acute abdomen
- Unexplained hypoglycemia
- Unexplained fever
- Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
- Hyperpigmentation or vitiligo
- Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal failure
Treatment of Acute Adrenal Crisis

- Treat and worry about diagnosis later (if the patient is not critically ill - ACTH stim test)
- Stat IV access, electrolytes, glucose, do not wait for lab results
- 2-3 L 0.9% Saline +- 5% Dextrose
- Stress-dose steroids
- Treat underlying medical conditions
Steroid Use

- First 24 hours:
  - Hydrocrotisone 100 mg every 6 hours
- Response: Rapid (improvement in <=12 hrs)
- Second day:
  - Hydrocortisone 50 mg every 6 h
- Third day:
  - Oral HC: 40 mg AM, 20 mg PM
- By Forth-fifth day taper to maintenance dosage
  - Oral HC 15-25 mg total daily in divided dosage
Mineralcorticoids Use

- In supra-physiological doses, HC has sufficient sodium-retaining potency
- So, additional mineral corticoid not required

- Other steroids & mineralcorticoid action
  - Prednisone (some with dosage higher >30 mg)
  - Dexamethasone (none)
Maintenance Therapy

- Life-long treatment
- Basal production rate of Cortisol
  - 8-12 mg/m²/d
- HC: 15-25 mg daily
- 10-15 mg AM - 5-10 mg PM
- Twice daily regimen gives satisfactory response
  - In most pts
HC 30 mg in Divided Dosage can be Supra-physiologic

Hydrocortisone 30 mg in Divided Doses is Supraphysiologic

Behan et al., Clin Endo, 2011
Hydrocortisone 10 mg (8 a.m.) and 5 mg (2 p.m.) more Closely Mimics Physiologic Cortisol Secretion in Hypopituitary Patients

Behan et al., Clin Endo, 2011
Importance of Avoiding Supraphysiological Dosage

- Filipson H et al JCEM 2006
  - 2000 pt: Higher A1C, Total Cholesterol, TG, waist circumferences with dose >= 25 mg
- Peacey et al Clin Endo 2006
  - 30% reduction in HC to 20 mg
  - 19% increase in bone formation marker
- Danilowicz K et al Pituitary 2008
  - 50% reduction from 30 mg to 15 mg
  - Decrease body fat, TG and increase quality of life
Additional Therapy

Other Steroids:

• Prednisone 3-5 mg daily
• Once daily dual-release hydrocortisone (not approved in US) (Johannsson G et al, JCEM 2012)
Additional Therapy

• Primary AI
  • Fludrocortisone 0.05-2 mg/d AM

• Too frequently neglected

• ~10% of Addisonian pt can be managed with diet alone
Educate Your Patient

- Advise every pt to register for a medical alert bracelet or necklace

- Regular education regards stress related steroid dosage adjustment which should involve the pt. partner and family as well

- Self-administration esp. for pt. living far from hospital
Sick Days Guidelines

Treatment of Minor Febrile Illness

- Increase glucocorticoid dose twofold to threefold for the few days of illness; do not change mineralocorticoid dose

- Contact physician if illness worsens or persists for more than 3 days or if vomiting develops

- No extra supplementation needed for uncomplicated, outpatient dental procedures with local anesthesia
Sick Days Guidelines

Emergency Treatment of Severe Stress/Trauma

- Inject contents of prefilled dexamethasone (4-mg) or HC (100 mg) syringe intramuscularly

- Get to physician as quickly as possible
Steroid Coverage for Illness or Surgery in Hospital

**Moderate Illness**
- Hydrocortisone 50 mg bid PO or IV
- Taper rapidly to maintenance dose as patient recovers

**Severe Illness**
- Hydrocortisone 100 mg IV q8h
- Taper to maintenance level by decreasing by half every day
- Adjust dose according to course of illness

**Minor Procedures under Local Anesthesia and Most Radiologic Studies**
- No extra supplementation needed
Steroid Coverage for Illness or Surgery in Hospital

**Moderately Stressful Procedures** (barium enema, endoscopy, or arteriography)

- Single 100-mg IV dose of hydrocortisone just before procedure

**Major Surgery**

- Hydrocortisone 100 mg IV just before induction of anesthesia
- Continue q8h for first 24 hr
- Taper dose rapidly, decreasing by half per day, to maintenance level
Therapeutic Use of Synthetic Corticosteroids

- Overuse?! Pt feels better?! Objective improvement in underlying disease?
- 1% of population is now prescribed long term corticosteroids therapy
- Decision regards use:
  - Evidence based
  - Constant review
  - Efficacy and side effects
Effect of Glucocorticoids

Endocrine system:
- LH, FSH release
- TSH release
- GH secretion

Eye:
- Glaucoma

Carbohydrate/lipid metabolism:
- Hepatic glycogen deposition
- Peripheral insulin resistance
- Gluconeogenesis
- Free fatty acid production
- Overall diabetogenic effect

GI tract:
- Peptic ulcerations

Cardiovascular/renal:
- Salt and water retention
- Hypertension

Adipose tissue distribution:
- Promotes visceral obesity

Bone and calcium metabolism:
- Bone formation
- Bone mass and osteoporosis

Skin/muscle/connective tissue:
- Protein catabolism/collagen breakdown
- Skin thinning
- Muscular atrophy

Growth and development:
- Linear growth

Immune system:
- Anti-inflammatory action
- Immunosuppression
Therapeutic Use of Synthetic Corticosteroids

- Providers need to be aware of the effects of long term therapy and of steroid withdrawal
- Suppression of the HPA axis is an important aspect of modern clinical practice
- Sudden cessation can result in adrenal failure
  - Most common cause of secondary adrenal insufficiency
HPA Axis Suppression

- Dosage
- Potency
- Half life
- Duration
- Daily vs. alternate days
- Time of intake: Morning vs. later
  - Greater suppression of early morning ACTH
### Comparison of representative glucocorticoid preparations

<table>
<thead>
<tr>
<th></th>
<th>Equivalent doses* (mg)</th>
<th>Relative antiinflammatory activity</th>
<th>Relative mineralocorticoid activity</th>
<th>Duration of action (hours)</th>
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<tr>
<td>Hydrocortisone (cortisol)</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>8 to 12</td>
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<tr>
<td>Cortisone acetate</td>
<td>25</td>
<td>0.8</td>
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<td>Prednisone</td>
<td>5</td>
<td>4</td>
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<td>12 to 36</td>
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<tr>
<td>Prednisolone</td>
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<td>4</td>
<td>0.8</td>
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<td>Methylprednisolone</td>
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<td>0.5</td>
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<td>Triamcinolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>12 to 36</td>
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<tr>
<td>Fludrocortisone</td>
<td>Not used for an antiinflammatory effect</td>
<td>10</td>
<td>125†</td>
<td>12 to 36</td>
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<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30</td>
<td>0</td>
<td>36 to 72</td>
</tr>
</tbody>
</table>

Prednisone and prednisolone are potent glucocorticoids and weak mineralocorticoids.
Steroids Less Than 3 Weeks

- Clinically significant HPA suppression is rarely a problem
- Withdraw suddenly with no ill effect
- Exception: frequent short courses of corticosteroids
Steroid More Than 3 weeks

- >= 15 mg equivalent of Prednisone: Inevitable
- 5-10 mg: Variable
- <5 mg: Reported clinically significant suppression, debatable
Long-Term Corticosteroid Therapy

- Treat them similar to your patients with ACTH deficiency
- Medics Alert card, bracelet or necklace
- Sick days guidelines
Recovery

- Might take up to 6-9 months
- CRH secretion return to normal within few weeks
- ACTH begins to increase, rising above normal range until adrenal steroidogenesis recovers
In The Interim...

- Patient may experience symptoms of adrenal insufficiency

- Anorexia, nausea, weight loss, arthralgia, lethargy, postural dizziness, ...
CAUTIOUSLY WITHDRAWN
Suggested Approaches

- Reduce rapidly to 7.5 mg equivalent
- Then 1 mg every 2-4 weeks OR
- Switch to hydrocortisone 20 mg/day
- Reduce by 2.5 mg every week to a level of 10 mg/day
Suggested Approaches

- In 2-3 months on reduced dosage:
  - Assess endogenous HPA function by ACTH stim test
  - Pass ----- withdrawn
  - Fail ------ continue
Patients Taking <5 mg >3 weeks

- Clinically significant HPA axis suppression Is ???
- If concerned
  - ACTH stim test done 12-24 hours after omitted steroid tx
- Immediate answer
- Sudden or gradual withdrawn
ADRENAL ADENOMAS, INCIDENTIOMAS, AND CARCINOMAS
INCIDENTILOMAS

- >1 cm
- Prevalence 1.5-7%
- Adrenal mass is uncovered up to 4% of patients imaged for non-adrenal pathology
- Uncommon <30 years
- Increase frequency with age
- Male = Female
Clinically

- 85% non-functional benign ADENOMAS
- Occ. they represent myelolipomas, hamartoma, granuloma infiltration...
Functional ADRENAL MASS

- Cortisol secreting adrenal ADENOMAS 6-10%
  - Subclinical Cushing
  - Cushing Syndrome
- Aldosterone secreting ADENOMAS
  - Hyperaldosteronism 0.6%
- Pure virilizing benign adrenal ADENOMAS: Rare ~50 cases
- Pheochromocytoma 3%
- Functional adrenal carcinoma
Work-up / Approach

All INCIDENTIOMAS should undergo appropriate endocrine screening test

All INCIDENTIOMAS should be tested for Subclinical Cushing and Pheochromocytoma

All INCIDENTIOMAS + Hypertension should be tested for aldosteroneoma
CLINICALLY

- Functional vs. non-functional
- Benign vs. malignant
Benign vs. Malignant Predictive

• Size:
  • <4 cm: Fewer than 2%
  • >6 cm: 25%
  • 4 cm cutoff: 93% sensitivity, limited specificity, therefore surgery in unilateral masses > 4 cm should be considered to avoid missing adrenal carcinoma

• Radiological characteristics
  • Smooth, homogenous, HU <10: Invariably benign
  • Irregular, heterogeneous, HU >20: Suspect malignancy
Malignancy

- Adrenal mets (known primary cancer, lung cancer)
- Primary Adrenal Carcinoma: Rare
- F>M: 2.5:1
- Mean age 40-50
- Most are functional:
  - Glucocorticoid alone (45%)
  - Glucocorticoid & androgens (45%)
  - Androgens alone (10%)
  - Aldosterone (<1%)
Adrenal Carcinoma Clinical Manifestation

- Features of the hormone excess state
- Abdominal pain
- Weight loss
- Anorexia
- Fever in 25%
- Palpable mass
- Metastatic spread
- Poor Prognosis
Cytology: FNA

- CANNOT distinguish benign adrenal mass from adrenal carcinoma

- CAN distinguish between adrenal tumor and Mets

- Can do only after excluding Pheochromocytoma with biochemical testing (hemorrhage and hypertensive crisis)
Glucocorticoids Excess

- Subclinical Cushing: glucocorticoid secretory autonomy, lack many of the usual stigmata, they may have HTN, DM/IGT, vertebral fracture, ...

- Cushing syndrome

- Adrenal Cushing ~ 10-15 % of hypercortisolemia etiology
Clinical Feature of Cushing Syndrome

<table>
<thead>
<tr>
<th>Findings</th>
<th>% of Patients</th>
<th>Discriminant Index</th>
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<tbody>
<tr>
<td><strong>Symptoms</strong></td>
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<tr>
<td>Weight gain</td>
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<td>Menstrual irregularity</td>
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<td>Hirsutism</td>
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<td>Psychiatric dysfunction</td>
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<td>Backache</td>
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<td>Muscle weakness</td>
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<td>Moon facies</td>
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<td>Red-purple striae</td>
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<td>Muscle weakness</td>
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<tr>
<td>Ankle edema</td>
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<td>Pigmentation</td>
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<td><strong>Other Findings</strong></td>
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<td>Hypertension</td>
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<td>Diabetes</td>
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<td>Renal calculi</td>
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</table>
Investigation When Suspected Cushing Syndrome

- TWO MAJOR STAGES

1- DOES YOUR PATIENT HAVE CUSHING SYNDROME (TRUE HYPERCORTISOLEMIA)?

2- IF THE ANSWER IS "YES", WHAT IS THE CAUSE?
Many investigators fail to make that distinction and jump to using testing that is relative to the second question.

And most importantly hold on radiological investigation until biochemical confirmation of the cause of Cushing Syndrome is obtained.
Circadian Rhythm: lost
Morning Cortisol is of no value
Random Cortisol if of no value
Midnight Cortisol: Sensitive and specific

Question 1: "Does Your patient Have Cushing Syndrome?"
Screening: Midnight Cortisol

- Late night salivary Cortisol
- CBG: Absent
- Sensitive and specific: 100%, 96% for overt Cushing,
  - Role to Dx Sub-clinical Cushing
- Non-invasive
- Does not require hospitalization
- False results
  - Disruption in day-night / wake-sleep cycle
Screening: Urinary Free Cortisol

- Free Cortisol
- Adequacy of collection: Simultaneous Creatinine secretion
- Limitation
  - Advanced renal disease
Screening: Low Dosage 1 mg Overnight Dexamethasone Suppression Test

- Cushing: Failure to suppress Cortisol levels to <5 ug/dL between 8-9 am the following morning
- Sensitive 95%, less specific
- False positive:
  - Phenytoin, rifampin (increase Dexamethasone clearance rate)
  - Factors affecting CBG
Question 2: “What Is The Cause Of Cushing In This Patient?”

- Morning plasma ACTH
- ACTH dependent: Normal to high
- ACTH independent: Suppressed
• ACTH independent ---- Adrenal imaging

• CT adrenal is the investigation of choice
To AVOID MISTAKES

- Adrenal images should not be performed unless biochemical evaluation confirm adrenal cause

- Incidentaloma: up to 7-10%
Treatment of Adrenal Cushing

- **Surgical**: Laparoscopic adrenalectomy: Unilateral tumors
- **Post surgery**: Treat with steroids as contralateral suppressed adrenal might take months to recover
Primary Hyperaldosteronism

Updates

- Most patients do not have hypokalemia
- Higher prevalence rate: 5-10% of all patients with hypertension (vs. 0.5%)
- Complete screening while your patient taking antihypertensive meds [except mineralcorticoid receptors antagonist: Aldactone, Eplerenone; discontinue at least 6 weeks before testing]
When to consider testing for primary aldosteronism:
- Hypertension and hypokalemia
- Resistant hypertension
- Adrenal incidentaloma and hypertension
- Onset of hypertension at a young age (<20 y)
- Severe hypertension (≥160 mm Hg systolic or ≥100 mm Hg diastolic)
- Whenever considering secondary hypertension

Morning blood sample in seated ambulant patient
- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or PRC

↑PAC (≥15 ng/dL)
↓PRA (<1.0 ng/mL per hour) or ↓PRC (<lower limit of detection for the assay)
and
PAC/PRA ratio ≥20 ng/dL per ng/mL per hour

Investigate for primary aldosteronism
Pheochromocytoma

- Men= Female. Third, Forth, Fifth decades
- Hypertension sustained or paroxysmal
- Spells:
  - Forceful heartbeat, tremor, headache, facial pallor, cool hand and feet, increase sense of body heat and sweating
  - Spontaneous or precipitated (postural change, anxiety, maneuvers that increase intra-abdominal pressure, lifting, exercise, colonoscopy, trauma, pregnancy
  - Usually 10-20 minutes
Pheochromocytoma

- FLUSHING is NOT typical for Pheochromocytoma

- Numerous disorders can cause signs and symptoms that may prompt the clinician to test for pheochromocytoma
### Endocrine Causes
- Carbohydrate intolerance
- Hyperadrenergic spells
- Hypoglycemia
- Pancreatic tumors (e.g., insulinoma)
- Pheochromocytoma
- Primary hypogonadism (menopausal syndrome)
- Thyrotoxicosis

### Cardiovascular Causes
- Angina
- Cardiovascular deconditioning
- Labile essential hypertension
- Orthostatic hypotension
- Paroxysmal cardiac arrhythmia
- Pulmonary edema
- Renovascular disease
- Syncope (e.g., vasovagal reaction)

### Psychological Causes
- Factitious (e.g., drugs, Valsalva)
- Hyperventilation
- Severe anxiety and panic disorders
- Somatization disorder

### Pharmacologic Causes
- Chlorpropanide-alcohol flush
- Combination of a monoamine oxidase inhibitor and a decongestant
- Illegal drug ingestion (cocaine, phencyclidine, lysergic acid diethylamide)
- Sympathomimetic drug ingestion
- Vancomycin ("red man syndrome")
- Withdrawal of adrenergic-inhibitor

### Neurologic Causes
- Autonomic neuropathy
- Cerebrovascular insufficiency
- Diencephalic epilepsy (autonomic seizures)
- Migraine headache
- Postural orthostatic tachycardia syndrome
- Stroke

### Other Causes
- Carcinoid syndrome
- Mast cell disease
- Recurrent idiopathic anaphylaxis
- Unexplained flushing spells
Most patients with spells do not have Pheochromyctoma

Most patients tested for Pheochromyctoma do not have it
Case Detection

Suspect if one or more of the following:

- Hyper-adrenergic spells (self-limited episodes of palpitations, diaphoresis, headache, tremor, or pallor)
- Resistant hypertension
- Familial syndrome (MEN2, NF1, VHL)
- Family history
- Incidentally discovered adrenal mass
- Pressor response during anesthesia, surgery or angiography
- Onset of hypertension at age <20 year
- Idiopathic dilated cardiomyopathy
Radiological Characteristics

- > 3 cm
- Round to oval with smooth margins
- Inhomogeneous
- Usually solitary / unilateral
- >10 HU
- Necrotic hemorrhage or calcifications: Common
- Growth 1 cm/year
Case Study

- 65 y/o F, intermittent abdominal pain
- Abdominal CT: Incidental 1.4 cm right adrenal mass, HU +2
- Denies other Sxs
- H/o fibromyalgia, hypertension (10 years)
- Meds: Propranolol 80 mg twice daily, Diltiazem 240 mg once daily, Hydrochlorothiazide 25 mg once daily, Cyclobenzaprine 10 mg daily
- PB 142/86, HR 68
Biochemical Picture

- Urine collection
- Metanephrine = 120 ug/24 H (<400)
- Normetanephrine = 1480 ug/24h (<900)
- Norepinephrine = 272 ug/24 H (<170)
- Epinephrine = 12 ug/24 H (<35)
- Dopamine = 366 ug/24 H (<700)
Next Step

- MIBG
- Measure plasma fractionated Metanephrine
- Discontinue Propranolol and re-measure urine studies in 2 weeks
- Something else?
Medications That May Cause False Positive Results

- Tricyclic antidepressants (including cyclobenzaprine)
- Levodopa
- Drugs containing adrenergic receptor agonists (e.g., decongestants)
- Amphetamines
- Buspirone and antipsychotic agents
- Prochlorperazine
- Reserpine
- Withdrawal from clonidine and other drugs (e.g., illicit drugs)
- Illicit drugs (e.g., cocaine, heroin)
- Ethanol
Adrenalectomy

- Functional unilateral tumor
- Suspicious imaging phenotype
- Tumors >4 cm
- Consider in Tumor that enlarges > 1 cm in diameter during follow up period
- Laparoscopic approach (shorter hospital stay, less complication), EXCEPT
  - In patient with highly suggestive adrenal carcinoma because breach of the tumor capsule is associated with poorer outcomes
Observation & Surveillance

- Non Functional smaller tumors
- There are no prospective studies of the optimal frequency and duration of follow up of adrenal incidentalomas
- The decision of the intervals between imaging, imaging frequency, should be guided by individual clinical circumstances, imaging phenotype and clinical judgment
- Suggest overnight DST be repeated annually for 4 years incase where initial evaluation was negative