Screening For Endocrine Disorders of the Adrenal, Pituitary, & Gonads

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Disclosures

• Contracted Research
  – Neurocrine Biosciences
  – Novartis Pharmaceuticals
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• Consultant
  – Laboratory Corporation of America
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  – Novartis Pharmaceuticals
  – Tokai Pharmaceuticals
  – Viamet Pharmaceuticals
  – Alder BioPharmaceuticals
  – Spruce Biosciences
Topics & Objectives

• Adrenal
  – Insufficiency
  – Primary Aldosteronism
  – Pheochromocytoma
  – Cushing’s
• Pituitary
  – Hypopituitarism & Hormone Excess
• Gonadal/Reproductive
  – Male Hypogonadism
  – Amenorrhea First Steps

Adrenal Insufficiency

Symptoms

• Weakness, fatigue 100%
• Anorexia 100%
• Nausea 86%
• Vomiting 75%
• Abdominal pain 31%
• Salt craving 16%
• Postural dizziness 12%
• Muscle or joint pain 6-13%
Adrenal Insufficiency

Signs & Labs

- Weight loss 100%
- Hyperpigmentation 94% (primary)
- Hypotension 88-94%
- Viteligo 10-20%
- Hyponatremia 88% (↓ Cortisol)
- Hyperkalemia 64% (↓ Aldosterone)

Adrenal Insufficiency

Diagnosis

- Basal (0800) Hormones Useful
  - Cortisol: <5 μg/dL Low; >15 μg/dL Normal
  - DHEA-S: >60 μg/dL Normal
  - ACTH: Low (<10 pg/mL) or High (>100)
  - Renin & Aldosterone
    - Primary AI: High Renin, Low Aldosterone
    - Secondary AI: Both Normal or High

- Cosyntropin Stimulation Test
  - 250 μg ACTH1-24 IM/IV
  - Cortisol@30-45 min: >18-20 μg/dL Normal
Diagnosis of Central AI: Ambulatory Setting

Baseline Serum Cortisol & DHEA-S

- Cortisol ≤5 μg/dL
  - Low DHEA-S
    - Confirm values; Investigate the cause; Start therapy

- Cortisol 6-12 μg/dL
  - Low DHEA-S
    - ITT
  - Normal DHEA-S
    - No further testing

- Cortisol >12 μg/dL
  - No further testing
Primary Aldosteronism

Whom To Screen?

• HTN + Spontaneous Hypokalemia
• Patients With Resistant HTN
• Patients With HTN At Age < 40
• Considering Secondary Causes
• HTN + Known Adrenal Mass

Primary Aldosteronism

Screening Procedure: Stop Drugs?

• Most Drugs OK for Screening
  – Most Drugs ↑PRA & Aldo (β-Blockers ↓PRA)
  – If PRA is Suppressed, Screen is Valid
• Up to 6 Wk: Spironolactone, Eplerenone
• Best: \( \alpha_1 \)-Blocker + Verapamil
• Can Always Rescreen After Off Drugs
**Primary Aldosteronism**

**Screening Tests**

- **Random PAC/PRA or “ARR”**
  - Try To Stimulate Renin Production in AM
  - PAC > 15 ng/dL **AND** PRA < 1 ng/mL•h
  - **PAC/PRA Dominated By Low PRA (÷0)**

- **24 h Urine Na, K**
  - Adequate Na Intake, **NO** K Supplements
  - K > 30-40 meq/d + Na > 100 meq/d
  - Useful if Hypokalemic

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**Pearl #3:** Screening is more about whether **renin** is **suppressed** than about whether aldosterone is high.
ARR Sensitivity & Specificity

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
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<tbody>
<tr>
<td>ARR &gt;20</td>
<td>78</td>
<td>83</td>
<td>56</td>
<td>93</td>
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<tr>
<td>ARR &gt;50</td>
<td>10</td>
<td>99</td>
<td>86</td>
<td>80</td>
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<tr>
<td>ARR &gt;20 and PAC &gt;15</td>
<td>57</td>
<td>88</td>
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</table>

Nishizaka 2005 Am J Hypertens 18:805

Who Has Primary Aldo?

ARR Interpretation

<table>
<thead>
<tr>
<th>Aldo (ng/dL)</th>
<th>PRA (ng/mL/h)</th>
<th>ARR</th>
<th>Serum Potassium (meq/L)</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>14</td>
<td>3.5</td>
<td>4</td>
<td>4.2</td>
<td>Low ARR, not PA</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>40</td>
<td>4.0</td>
<td>Low aldo, not PA</td>
</tr>
<tr>
<td>21</td>
<td>0.6</td>
<td>35</td>
<td>4.1</td>
<td>Positive screen,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>go to confirmatory testing</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
<td>20</td>
<td>3.3</td>
<td>Probably PA,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>supplement K, rescreen</td>
</tr>
<tr>
<td>38</td>
<td>2.0</td>
<td>19</td>
<td>3.7</td>
<td>Probably PA,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>stop meds &amp; rescreen</td>
</tr>
</tbody>
</table>
Pheochromocytoma
Clinical Features

- Pressure: Sustained HTN + Spikes
- Pain: Throbbing HA, Chest Pain
- Perspiration: Heavy, Generalized
- Palpitations
- Pallor
- Other: Hyperglycemia, Weight Loss, Tremor, Orthostasis, Hypercalcemia, Fatty Liver, Cardiomyopathy
- 5-10% Asymptomatic(!!)

Catecholamine Catabolism

Norepinephrine

Epinephrine

Normetanephrine

Metanephrine

Vanillylmandelic Acid (VMA)

COMT

MAO
Pheochromocytoma Screening Tests

- 24 h Urine Metanephrines & Catecholamines
  - MN >400 μg, NMN >900 μg; Epi >35 μg, NE >170 μg
- Plasma Metanephrines: More False Positives
  - Seated 5 Min; Indwelling Catheter Best
  - NMN >0.9 nM ~ 150 pg/mL, MN >0.5 nM ~ 60 pg/mL
  - No Caffeine, Acetaminophen, TCA, SSRIs, Labetalol, Sotalol, Phenoxybenzamine (Although Usually OK)
- Grossly Positive Screen Sufficient (Clonidine)
- Most Slightly Abnormal Screens Not Pheo

Pearl #1: Pheo Symptoms Correlate With Catecholamine Elevations
Pearl #2: Pheos Do Not Hide on CT Scans

CT: Pheochromocytoma
Cushing Syndrome – Exam

Discriminatory Features

• Proximal Muscle Weakness/Myopathy
• Wide, Purple, Nonblanching Striae
• Easy Bruising
• Dermal Atrophy
• Disproportionate Supraclavicular Fat
• Poor Sleep
• Unexplained Hyperglycemia or Osteoporosis

➢ Findings Increase Pre-Test Probability

Cushing Syndrome

Principles of Testing

• Cortisol Production is Elevated
  – Urinary Free Cortisol
  – Not Always High, Varies With Assay
• Cortisol Production is Not Suppressible
  – Dexamethasone Suppression
  – Most Sensitive for ACTH-Independent
• The Diurnal Rhythm is Blunted
  – Nocturnal Serum or Saliva Cortisol
  – Saliva Cortisol Now Routine
Cushing Syndrome
Screening Tests: 24 h UFC

- Cortisol Cleared Only When Concentration Exceeds Plasma Binding Capacity
- “Free” Cortisol Not CBG-Bound
- False Positives: High Urine Volumes
  - Pseudocushing: EtOH, Obesity, Stress, Psyc
- False Negatives: Undercollection, Early Dz

UFC: What Are We Measuring?

CPR: 6-8 mg/m²/d

THF, aTHF, THE, aTHE, Cortisone, Cortolones, Cortols, 11OH-Androsterone, 6β-OH-Cortisol, etc, etc...

~10 mg/d = UFC

Cortisol

Cortisol•CBG
Cushing Syndrome
Screening Tests: Dexamethasone

- 1 mg Overnight DST
  - 1 mg Dexamethasone at 2300
  - 0800 Cortisol >1.8 μg/dL (Prior >5 μg/dL)
- False Positives:
  - Pseudocushing States; Estrogen (CBG)
  - Rapid Dex Metabolism (Rifampin)
- False Negatives: CYP3A4 Inhibitors

Cushing Syndrome
Nocturnal Cortisol Testing

- Late Night Cortisol Sampling
  - Midnight Cortisol >7.5 μg/dL Diagnostic (?)
  - Requires Admission, IV Catheter
- Outpatient Saliva Cortisol
  - Reflects Plasma Free Cortisol
  - Normally Obtain 2-3 at 2300-2400
  - Values <100 ng/dL Normal
  - Values >250 ng/dL C/W Cushing’s
Pituitary Testing
General Principles

• If You Think It Is High, Try To Suppress
  – Or Measure When It Should Be Low
• If You Think It Is Low, Try To Stimulate
  – Or Measure When It Should Be High
• Normative Data Or Lack Thereof
  – Assays & Populations Used For Data
• Typical Loss-of-Function Order w/Tumor
  – GH>LH/FSH>TSH>ACTH; AVP Hypothalamus
Central Hypothyroidism

• Pitfall of Screening with TSH Only
• Inappropriate Normal/Low TSH + Low FT4
• TSH Receptor is “Noisy”
  – Free T4 Rarely Falls to <0.5 ng/dL

Growth Hormone Deficiency

Basal Testing

• IGF-1: Good Screen
  – Age, Gender, Tanner Stage Ranges
  – May Be Sufficient, Especially If MPHD
  – Normal Value Does Not Exclude GHD
• IGFBP3: Slightly More Specific
  – Utility In Children Only
• Random GH of No Utility in Adults
Vasopressin Deficiency (DI)

- Neurogenic (Central)
  - Parital
  - Complete
- Nephrogenic
  - Parital
  - Complete
- Dipsogenic Polydipsia
  - Dipsogenic (Thirst)
  - Psychogenic (No Thirst)
Diagnosis of DI

- **Complete DI**
  - Inability to Concentrate Urine
  - $S_{osm} > U_{osm}$ and $> \sim 300$ mOsm/kg
  - Thirst Center Activated 292 mOsm/kg
  - Dehydration Test Rarely Necessary
- **Partial DI**
  - $U_{osm} > S_{osm}$ and $< 295$ mOsm/kg
  - ***The Ability to Concentrate Urine Does Not Exclude a Deficiency of Vasopressin***

Hormone Excess

- **Prolactin**: Basal Only (Stress FP)
- **GH**: Basal IGF-1 +/- GH
- **TSH**: Non-Suppressed + High T4
  - FAS/TSH Molar Ratio $> 1$
  - $= [FAS (\mu g/L) / TSH (mU/L)] \times 10$
- **LH/FSH**: “Non-Secreting Tumors”
Male Reproduction Physiology

- GnRH
- LH
- FSH
- Leydig Cells
- Sertoli Cells
- Testosterone
- Estradiol
- Aromatase
- Spermatogenesis
- Inhibin

Normal Range

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Normal Range (ng/dL)</th>
<th>Deficiency (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T</td>
<td>250 - 900</td>
<td>&lt;250</td>
</tr>
<tr>
<td>Free T</td>
<td>5 - 20</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Bioavailable T</td>
<td>100 - 400</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

Free/Bioavailable T:
- Aging (high SHBG)
- Obesity (low SHBG)
- Borderline Total T (200-300)
Diagnosing T Deficiency

• Screening Test:
  – Total Serum Testosterone by 0900

• If Abnormal or Low-normal, Repeat:
  – Free Testosterone and/or SHBG
  – Bio-T By Calculation <100 ng/dL
  – http://www.issam.ch/freetesto.htm
  – LH and FSH
  – Prolactin

Before You Start…

<table>
<thead>
<tr>
<th>Month</th>
<th>Testosterone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>236</td>
<td>238</td>
</tr>
<tr>
<td>3</td>
<td>219</td>
<td>207</td>
</tr>
<tr>
<td>6</td>
<td>217</td>
<td>196</td>
</tr>
<tr>
<td>9</td>
<td>206</td>
<td>188</td>
</tr>
<tr>
<td>12</td>
<td>203</td>
<td>191</td>
</tr>
</tbody>
</table>
Female Reproductive Axes

- GnRH → LH
- LH → Theca Cells
  - Androstenedione
- LH → Granulosa Cells
  - Estradiol
  - Inhibin
  - Ovulation

Oligo- Amenorrhea

Definitions

- Primary: No Menses By Age 16
  - Or By Age 14 Without Secondary Sex Char
- Secondary: No Menses For 3 Mo
- Categories:
  - Anatomic Defect
  - Ovarian Failure
  - Chronic Anovulation With Estrogen
  - Chronic Anovulation Without Estrogen
Oligo- Amenorrhea
Sites Of Dysfunction

- Hypothalamus & Higher Brain Centers
- Pituitary
- Ovaries
- Uterus
- Outflow Tract

Oligo- Amenorrhea
History

- Puberty, Prior Menses & Pregnancies
- PMH, Meds, STDs
- D&C – Why, Volume Removed
- Moliminal Sx
- Infections, Trauma, Contraception
- Weight Change, Virilization
- Galactorrhea, Hot Flashes, Vision
Oligo- Amenorrhea

Physical Exam
• Ht & Wt; Tanner Stage; Turner Stigmata
• Visual Fields, Galactorrhea
• Virilization, Hirsutism, Striae, Acne
• Carotenemia, Acanthosis Nigricans

Oligo- Amenorrhea

Laboratory
• hCG, hCG, hCG
  – ON EVERYBODY, NO EXCUSES
• FSH, Prolactin, TSH/FT4
• Karyotype If Short
• Basal Body Temperature Very Useful
• Progestin Challenge (Tanner 4-5)
  – 5 mg MPA x 10 d or 10 mg x 5 d
  – Micronized Progesterone 200 mg x 12 d
Oligo- Amenorrhea
Progestin Challenge

• Withdrawal Bleeding Indicates
  – Estrogen Exposure
  – Functional Endometrium
  – Patent Outflow Tract
  – Suggests Ovarian Or Partial Central D/O

• No Withdrawal Bleeding Indicates
  – No Estrogen Production (Trial OCP) –OR–
  – Outflow Tract Obstruction

Amenorrhea

History
Exam
hCG

Prolactin
TSH+FT4
FSH

Pubertal Failure
Pregnancy
Systemic Disease

Pituitary Disease
Thyroid Disease
Ovarian Failure

Anatomic Defect
Chronic Anovulation
+/- Estrogen
Summary

• Basal Testing Useful if Performed Well
• Primary Aldosteronism is Common
• Cushing’s is Difficult
• Amenorrhea Initial Evaluation