The Evaluation of the Incidental Adrenal Mass and Not-So-Incidental Adrenal Hormone Excess

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Disclosures

• Contracted Research
  – Millendo Therapeutics
  – Novartis Pharmaceuticals
  – Strongbridge Biopharma

• Consultant
  – Laboratory Corporation of America
  – Corcept Therapeutics
  – Janssen Pharmaceuticals
  – Novartis Pharmaceuticals
  – Innocrin Pharmaceuticals
  – Diurnal, LTD
  – Alder BioPharmaceuticals
  – Spruce Biosciences
Magnitude of the Problem

- Adrenal Nodules Found in 1-7% of CT Scans Performed for Unrelated Reasons
  - Prevalence Increases with Age, H/O CA
- US Population >300,000,000
  - ~3-21 Million Adrenal Nodules
- ~4,000 Endocrinologists in USA
- If All Endocrinologists Saw 8/Week, It Could Take Up To 15 Yr To See All(!!)
Adrenal CT: Normal Glands
CT: Typical Adrenal Nodule
Incidental Adrenal Nodules

Differential Diagnosis

- “Nonfunctioning” Cortical Adenoma
- Cortisol-Producing Adenoma/Nodular Disorders
- Aldosterone- or DOC-Producing Adenoma
- Adrenocortical Carcinoma
- Pheochromocytoma
- Myelolipoma
- Cyst
- Metastatic Carcinoma
- Lymphoma
- Infection/Granululoma
- Hemorrhage
- Congenital Adrenal Hyperplasia
Incidental Adrenal Nodules

Non-Adrenal Tumors

- Renal Cysts and Masses
- Accessory Spleen
- Gastric Duplication
- Ganglioneuromas
- Retroperitoneal Tumors
Three Parts Of The Evaluation

• Look at the Scan
  – Size, Imaging Characteristics
  – The OTHER Adrenal

• Interview & Examine the Patient
  – History, Physical Exam, Recent Changes

• Laboratory Evaluation
  – Routine & Directed Testing
Part 1: Imaging Data

- **Size:** <2, 2-4, >4 cm Useful Gauge
- **Noncontrasted CT Density**
  - <10 HU = Lipid-Rich Adrenocortical Tumor
  - Might Cause Hormone Excess
- **Homogeneity or Lack Thereof**
- **Contrast Enhancement**
  - Amount, Pattern, Washout
- **Other Suspicious Features**
  - Lymph Nodes, Invasion, IVC Thrombus
Large is Bad
Adrenocortical Cancer
CT: Pheochromocytoma
Large, Heterogeneous
Part 1: Ancillary Imaging Data

- MRI: Signal Loss on Out-of-Phase Images = High Lipid Content
  - Not Routinely Necessary
  - High Signal on T2-Wtd = Pheo, Other
- $^{123}$I-MIBG, $^{111}$In-Pentotretotide SPECT/CT
  - Should Follow Biochemical Testing
- $^{18}$F-FDG, $^{68}$Ga-DOTATATE PET/CT
  - Question of CA, Metastasis
  - Preferable to Biopsy Most Cases
  - 10% of Benign Tumors PET-Avid (Pheo)
Pheo: Hyperintense On T2-MRI
Incidental Adrenal Nodules
Part 2: History & Physical

- Cushing’s Stigmata: SC/DC Fat Pads, Thin Skin & Bruising, Muscle Weakness, Plethora
- Androgen Excess (Women)?
Cushing Syndrome
Common Features

- Central Obesity
- Metabolic: ↑Glucose, ↑TG; ↓K; HTN
- Women: Amenorrhea, Hirsutism
- Depression, Psychosis
- Dorsocervical Fat Pad
  - Supraclavicular More Specific
- Children: Growth Impairment
Cushing Syndrome
Discriminatory Features

• Proximal Muscle Weakness/Myopathy
• Osteoporosis
• Wide, Purple Striae
• Easy Bruising
• Supraclavicular Fat Pads
  – Disproportionate Head & Neck Fat
• Facial & Upper Chest Plethora
Incidental Adrenal Nodules
Part 3: Basic Laboratory Evaluation

• Screen For Cushing’s
  – 1 mg ONDST, <1.8 μg/dL = 50 nmol/L
  – 24 h UFC Poor Sensitivity For Early Cushing’s
  – Additional Testing if Suspicious

• Screen For Pheochromocytoma
  – 24 h Urine or Plasma Metanephrines
  – Plasma More Sensitive But Less Specific
  – Avoid Caffeine, Acetaminophen, TCA, SSRIs, Phenoxybenzamine, Levodopa
  – >2x ULN Urine, >1 nmol/L Plasma = Positive
    ****Most Slightly Elevated NorMN = False Positive

• Screen For Primary Aldo if HTN &/or Low K
Catecholamine Catabolism

Norepinephrine → Normetanephrine → Vanillylmandelic Acid (VMA)

Epinephrine → Metanephrine → MAO

COMT
Case 1

- 58 YO WM, Single Episode Hematuria
- No Paroxysms, NI BP
- US: R Adrenal Mass
- 24 h Urine MN 233 mcg, NMN 2504 mcg
- MRI: 3.4 cm R adrenal mass
  - High, Heterogeneous Signal T2-weighted
  - No Signal Drop-out Out-of-phase T1
- Plasma MN, NMN 0.45 & 7.65 nmol/L
Case 1: CT Scan
Cushing Syndrome
Principles of Testing

• Cortisol Production is Elevated
  – Urinary Free Cortisol

• The Diurnal Rhythm is Blunted
  – Serum/Saliva Cortisols at Night

• Cortisol Production Not Suppressible
  – Dexamethasone Suppression Tests

• Distinguish From Pseudocushing State

• ACTH-Dependent or Independent
SCS & Adrenal Nodules

- **Who To Screen More Carefully**
  - >2 cm Adrenal Mass
  - Clinical Findings: Bruising, SC Fat Pads
  - Recent Changes: DM, HTN, Fat Redistribution

- **How To Test**
  - Early AM ACTH, Random DHEAS, ON-DST
  - 24h UFC, Nocturnal Saliva Cortisol Insensitive
  - Repeat, REPEAT, **REPEAT**

- **Surgery Improves Morbidities in SCS**
  - Primarily HTN, Glucose Tolerance IF PRESENT
Discordance In Commercial ACTH Assays

Case 2

- 37-yo WF, New Onset HTN, IFG
- CT: 2.3 cm Left Adrenal Mass
- Mild Weight Gain, Regular Menses
- PE: Mild Facial Plethora, Moon Facies, Dermal Atrophy, SC Fat Pads, Central Obesity

<table>
<thead>
<tr>
<th></th>
<th>10/2013</th>
<th>5/2014</th>
<th>10/2014</th>
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<tbody>
<tr>
<td>ACTH</td>
<td>14</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>DHEAS</td>
<td>126</td>
<td>71</td>
<td>41</td>
</tr>
<tr>
<td>ONDST</td>
<td>1.4</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Macronodular Hyperplasia
Case 3: History

• 50 y/o WF G5P3, Worsening Hirsutism
  – Mostly Upper Arms
• Menses Age 16 & Regular, Now Scant
• Hirsutism Age 16, Rx Electrolysis
  – Cleared chin/moustache/sideburns/nipples
  – By 30s Needed Electrolysis on Abdomen
• Testosterone = 179 ng/dL (nl <50)
• CT: No Adrenal Tumor -- BUT
Case 3: Lab Data

- Repeat Testosterone 121 ng/dL
- SHBG 52 nmol/L
- DHEA-S 427 mcg/dL
- Basal 17OHP 1,144 ng/dL
  - After Cosyntropin >17,000 ng/dL

Diagnosis: Nonclassic 21OHD
Incidental Adrenal Nodules
Follow-Up Recommendations

- Directed Annual History And Physical
- Repeat Screening: Index Of Suspicion
- Repeat Imaging As Indicated
  - Probably Everyone In 1 Year, Stop If Stable
  - Larger Nodules Sooner/More Frequently
- Indications For Surgery
  - Hyperfunction Or Mass Effect
  - Size >6 cm (?3 cm) Or Worrisome Features
  - >3 cm Often Subtle Cortisol Excess
Subclinical Cushing Syndrome
Mild ACTH-Independent Hypercortisolism

- ~25% Subtle Cortisol Excess (SCS)
- Evident On Careful Testing
- 90% Have Hypertension
- 50% Have DM, Dyslipidemia, Obesity
- 10% Progress to Overt Cushing Syndrome
- Prevalence Higher if >2.5 cm
Association between osteoporosis/VCF and Subclinical Hypercortisolism (SH)

Effect of Mild Cushing syndrome (CS) on Mortality

- **Di Dalmazi (2014):** retrospective, single-center study of 198 consecutive patients with adrenal incidentaloma. Mean f/u 7.2 years
- 34% baseline and 43% at study end had dysregulated cortisol
- Mean follow-up period 7.5 years; mean age range 61-70 years

Di Dalmazi: Higher mortality in patients with subclinical CS

Kaplan-Meier analysis: mortality by status at follow-up

- Worsened
- Stable intermediate phenotype/subclinical Cushing’s syndrome (Stable IP/subclinical CS)
- Stable non-secreting

All-cause mortality

Cardiovascular-specific mortality

<table>
<thead>
<tr>
<th>Status</th>
<th>Follow-up (years)</th>
<th>2014</th>
<th>2019</th>
<th>2024</th>
<th>2029</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable non-secreting</td>
<td></td>
<td>114</td>
<td>94</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Stable IP/subclinical CS</td>
<td></td>
<td>61</td>
<td>41</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Worsened</td>
<td></td>
<td>23</td>
<td>16</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Association of SH with CV Events

- Morelli (2014): retrospective multicenter study of 206 patients with adrenal incidentaloma and no overt signs of hypercortisolism
- Minimum follow-up period 5 years (median 72.3 months)
- Positive SH diagnosis if:
  - 1-mg DST cortisol >5 μg/dL - OR -
  - At least 2 of the following: ACTH <10 pg/mL and/or UFC >ULN and/or 1-mg DST cortisol >3 μg/dL

<table>
<thead>
<tr>
<th>SH patients were older and had larger adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without SH</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>167 (81.1%)</td>
</tr>
<tr>
<td>Mean age, y</td>
</tr>
<tr>
<td>58.5</td>
</tr>
<tr>
<td>Adenoma diameter, cm</td>
</tr>
</tbody>
</table>

Increased Cardiovascular Event (CVE) in SH

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio (OR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent CVE</td>
<td>3.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Incident CVE</td>
<td>2.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Worsening metabolic profile*</td>
<td>3.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Increase in at least 2 parameters: body weight, blood pressure, glycemia, and/or LDL cholesterol

- Risk of incident CVE: Adenoma diameter >2.4 cm and DST cortisol >1.8 μg/mL confers elevated risk, even in the absence of SH

1-mg DST cortisol levels with the best sensitivity and specificity for predicting incident CVE

Cortisol as a Marker for Increased Mortality in Patients with Incidental Adrenocortical Adenomas

206 patients consecutive patients with incidental adrenal nodule (benign) 2005-2013 with mean f/u 4.2 yrs

Overnight 1 mg DST:
- <1.8 µg/dL (n=95)
- >1.8 µg/dL (n=111)

Kaplan-Meier survival curve according to post-dex cortisol excluding extra-adrenal malignancy

## Postoperative Changes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy Bruising</td>
<td>100% (9/9)</td>
</tr>
<tr>
<td>Facial Plethora</td>
<td>100% (3/3)</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>89% (8/9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75% (6/8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>67% (2/3)</td>
</tr>
<tr>
<td>Significant Fatigue</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>Proximal Weakness</td>
<td>75% (6/8)</td>
</tr>
<tr>
<td>Abnormal Fat Pads</td>
<td>63% (5/8)</td>
</tr>
</tbody>
</table>

*Mitchell et al 2007 Surgery 142:900*
Mild Adrenal Cushing Syndrome
Surgical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>SH+ treated (n = 25)</th>
<th>SH+ untreated (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BW (kg)</td>
<td>77.3 ± 20.4 (52–129)</td>
<td>75.0 ± 14.8 (53.7–97.5)</td>
</tr>
<tr>
<td>18-months BW (kg)</td>
<td>76.3 ± 21.2 (51–140)</td>
<td>75.6 ± 14.8 (55–102)</td>
</tr>
<tr>
<td>Last follow-up BW (kg)</td>
<td>75.1 ± 19.1 (49–123)</td>
<td>76.1 ± 14.9 (55–103)</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>134.9 ± 16.4 (105–170)</td>
<td>129.9 ± 9.4 (125–135)</td>
</tr>
<tr>
<td>18-months SBP (mm Hg)</td>
<td>122.8 ± 11.6 (105–155)</td>
<td>140.6 ± 17.4 (110–170)</td>
</tr>
<tr>
<td>Last follow-up SBP (mm Hg)</td>
<td>123.9 ± 11.5 (110–155)</td>
<td>139.4 ± 14.2 (132–147)</td>
</tr>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td>81.8 ± 10.5 (60–115)</td>
<td>77.0 ± 6.5 (74–80)</td>
</tr>
<tr>
<td>18-months DBP (mm Hg)</td>
<td>74.3 ± 7.9 (60–89)</td>
<td>84.4 ± 12.1 (110–170)</td>
</tr>
<tr>
<td>Last follow-up DBP (mm Hg)</td>
<td>75.5 ± 7.3 (65–85)</td>
<td>83.1 ± 10.0 (78–88)</td>
</tr>
<tr>
<td>Baseline FG (mg/dL)</td>
<td>98.9 ± 18.9 (72–137)</td>
<td>92.6 ± 12.6 (74–129)</td>
</tr>
<tr>
<td>18-month FG (mg/dL)</td>
<td>89.3 ± 12.0 (74–130)</td>
<td>114.6 ± 37.3 (73–195)</td>
</tr>
<tr>
<td>Last follow-up FG (mg/dL)</td>
<td>90.0 ± 14.6 (74–138)</td>
<td>113.6 ± 37.8 (73–190)</td>
</tr>
<tr>
<td>Baseline LDL (mg/dl)</td>
<td>141.1 ± 38.3 (65–223)</td>
<td>124.5 ± 38.6 (77–200)</td>
</tr>
<tr>
<td>18-months LDL (mg/dl)</td>
<td>124.1 ± 37.8 (52–201)</td>
<td>125.2 ± 19.8 (102–169)</td>
</tr>
<tr>
<td>Last follow-up LDL (mg/dl)</td>
<td>124.9 ± 39.7 (52–201)</td>
<td>125.5 ± 19.5 (102–169)</td>
</tr>
</tbody>
</table>

Chiodini et al 2010 JCEM 95:2736
Primary Aldosteronism

Key Points

- Most Common Cause of Secondary HTN
- High End-Organ Damage
- Curable or Targeted Therapy
- Low Rates of Screening & Diagnosis
  - Fear of Embarking On Workup
  - Confusion About Approach
  - <1% Ever Screened
- Syndrome With Many Etiologies
Patients with Hypertension that are at Increased Risk for PA

PA Unlikely

ARR to Detect Cases (1|⊕⊕⊙⊙)

+ ↓ K⁺, renin ↓↓↓
PAC > 20 ng/dL

Patient Unwilling/Unable to Proceed

PA Unlikely

Confirmatory Testing (1|⊕⊕⊙⊙)

+ No Need for Confirmatory Testing (2|⊕⊙⊙⊙)ᵇ

Treat with MR Antagonist (2|⊕⊕⊙⊙)ᵃ

↓ K⁺, renin ↓↓↓
PAC > 20 ng/dL

Patient Unwilling/Unable to Proceed

Adrenal CT (1|⊕⊕⊕⊙)

If Surgery Desired

AVS (1|⊕⊕⊕⊙)

Marked PA, Young Age, and + CT (2|⊕⊙⊙⊙)ᶜ

Bilateral

Treat with MR Antagonist (1|⊕⊕⊕⊙)

Unilateral

Treat with Laparoscopic Adrenalectomy (1|⊕⊕⊕⊙)

Subtype Testing

If Surgery Not Desired

Funder et al 2016 JCEM 101:1889
Primary Aldosteronism
Whom To Screen?

- HTN + Hypokalemia
- Patients With Resistant HTN
  - Or Controlled With 4 Drugs
- Patients With HTN At Age < 40
  - Or FH HTN or CVA Age <40
- Considering Secondary Causes
- Sustained BP >150/100
- HTN + Known Adrenal Mass or OSA
- HTN + First-Degree Relative With PA
Primary Aldosteronism
Screening Procedure: Stop Drugs?

• Most Drugs OK for Screening
  – Most Drugs $\uparrow$PRA & Aldo ($\beta$-Blockers $\downarrow$PRA)
  – If PRA is Suppressed, Screen is Valid

• Up to 4 Wk: Spironolactone, Eplerenone
  – BUT STILL OK if PRA Suppressed

• Best: $\alpha_1$-Blocker + Verapamil

• Can Always Rescreen After Off Drugs
ARR Sensitivity & Specificity

Nishizaka 2005 Am J Hypertens 18:805
Who Has Primary Aldo?

ARR Interpretation

<table>
<thead>
<tr>
<th>Aldo</th>
<th>PRA</th>
<th>ARR</th>
<th>$K^+$</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>3.2</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>30</td>
<td>4.2</td>
</tr>
<tr>
<td>11</td>
<td>0.8</td>
<td>15</td>
<td>2.8</td>
</tr>
<tr>
<td>20</td>
<td>&lt;0.6</td>
<td>&gt;33</td>
<td>3.3</td>
</tr>
<tr>
<td>38</td>
<td>2.0</td>
<td>19</td>
<td>3.5</td>
</tr>
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</table>
Primary Aldosteronism
Where Progress is Needed

• Getting Patients Screened
• Simplify Confirmatory Testing
• Secondary Criteria for AVS
• Other Ways to Identify Who Has Bilateral Disease & Does NOT Need CT & AVS
• Titrating Medical Therapy
• Dealing With The Heterogeneity of PA
Adrenals Are Life;
The Rest is Just Details