“Adrenal Apoplexy”

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"Adrenal Apoplexy"

- Dictionary.com
- Apoplexy
  - A stroke
  - A sudden usually marked loss of bodily function due to rupture or occlusion of a blood vessel
  - A hemorrhage into an organ or tissue

Glomerulosa

- Aldosterone (salt)

Fasciculata

- Cortisol, deoxycorticosterone (sugar)

Reticularis

- Androgens (sex)
Case History 1:

• A 55 year old male has vague abdominal pain. He has a 10 year history of HTN. A CTS shows a 4 cm adrenal mass.
Question 1: The next step in management will include

- A) FNA biopsy
- B) Serum calcium and PTH levels
- C) Urinary 5-hydroxyindoleacetic acid
- D) Wait 6 months and repeat CTS
- E) 1 mg Dexamethasone suppression test
Question 1: The next step in management will include

- A) FNA biopsy
- B) Serum calcium and PTH levels
- C) Urinary 5-hydroxyindoleacetic acid
- D) Wait 6 months and repeat CTS
- E) 1 mg Dexamethasone suppression test
Adrenal Incidentaloma

- Definition: otherwise unsuspected adrenal mass on imaging
  - Excludes patients imaged as work up for cancer
- Up to 8.7% autopsy series
Adrenal Incidentaloma

3 questions

• Is the tumor hormonally active?
• Does the tumor have the radiographic characteristics of a malignancy?
• Does the patient have a history of cancer?
Adrenal Incidentaloma

Differential

- Nonfunctional: 80%
- Hypercortisolism: 5% Subclinical Cushing’s Syndrome (SCS)
- Aldosteronism: 1%
- Pheochromocytoma: 5%
- Adrenal Cortical Cancer 5%
- Other
  - Ganglioneuromas, Myelolipomas, Benign cysts
- Metastasis: 2.5%
Case History 4

• 51 year old female has HTN, weight gain, diabetes, and easy bruising. She has a BP of 154/95, weighs 250 lbs., and a characteristic buffalo hump. The diagnosis of Cushing’s syndrome is made.
Question 4: Which of the following statements is true

- A) Ectopic ACTH secretion is most commonly due to medullary thyroid cancer
- B) Cushing’s disease is the most common cause of endogenous Cushing’s syndrome
- C) An elevated 24 hour urinary cortisol is diagnostic for Cushing’s disease
- D) The most accurate test to rule out exogenous Cushing’s syndrome is a C-peptide level
- E) An adrenal adenoma is the most common cause of ACTH dependent Cushing’s syndrome
Question 4: Which of the following statements is true

- A) Ectopic ACTH secretion is most commonly due to medullary thyroid cancer
- B) Cushing’s disease is the most common cause of endogenous Cushing’s syndrome
- C) An elevated 24 hour urinary cortisol is diagnostic for Cushing’s disease
- D) The most accurate test to rule out exogenous Cushing’s syndrome is a C-peptide level
- E) An adrenal adenoma is the most common cause of ACTH dependent Cushing’s syndrome
Adrenal Incidentaloma Screening

• Hypercortisolism
  – 1 mg Dexamethasone suppression test
    • AM serum cortisol > 5.0 mcg/dl
    • Suppression < 1.8 mcg/dl (best NPV)
  – Low ACTH, DHEAS
  – Second confirmatory test
    • Evening salivary cortisol, 2 day low dose dexamethasone suppression test, 24 hour urine cortisol

Zeiger et al Endocrine Practice 2009
Adrenal Incidentaloma Screening

• Aldosteronism (if hypertensive)
  – PAC/PRA > 30, PAC > 20 ng/dl
  – Confirm with lack of suppression with salt loading

• Pheochromocytoma
  – Plasma free metanephrine and normetanephrine (higher false +)
    • > 3-4 times normal
  – 24 hour urine metanephrines (higher false -)
    • > 1800 mcg
  – Always before needle biopsy
  – Always before resection
  – RET, VHL, Succinate dehydrogenase genes

Zeiger et al Endocrine Practice 2009
Adrenal Incidentaloma

**Radiologic Imaging**

- Density measurement on non contrast CTS or in phase and out of phase MRI
  - Intracellular lipid
  - < 10 HU
- Contrast washout kinetics on CTS
  - Immediate after contrast
  - 10-15 delay
  - > 50% washout
- Size, homogeneity, borders, metastasis

Zeiger et al Endocrine Practice 2009
Adrenal Incidentaloma

Follow up

- Imaging
  - 3-6 months
  - Yearly 1-2 years
- Hormone evaluation
  - Annually up to 5 years

<table>
<thead>
<tr>
<th>Follow up (years)</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>Imaging growth</td>
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<tr>
<td>Hormonally active</td>
<td>17</td>
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</tbody>
</table>

Zeiger et al Endocrine Practice 2009
Subclinical Cushing’s Syndrome

- Natural history is poorly known
- Progression to overt Cushing’s rare
- Long term morbidity and mortality data do not exist
- No long term data for medical management
- Controversial: young patient with recent onset or worse co-morbidity
Cushing’s Syndrome

- Exogenous Steroids
- ACTH Dependent (80%)
  - Pituitary adenoma (Cushing’s disease) 70%
  - Ectopic ACTH 15%
  - Ectopic CRH Rare
- ACTH Independent (20%)
  - Cortisol producing adenoma 10%
  - Cortisol producing adrenal carcinoma 5%
  - Bilateral adrenal hyperplasia Rare
  - Macronodular hyperplasia Rare
Hypercortisolism

*Perioperative Management*

- High risk DVT
- Suppressed HPA axis
  - Glucocorticoid replacement 6-18 months
Case History 3

• 44 year old female reports pounding headaches, flushing, and hypertension for 12 months. She has elevated urinary catecholamines and metanephrines. There is no family history of endocrinopathy. CTS shows a 5 cm adrenal mass.
Question 3: You advise which management:

- A) Bilateral adrenal vein sampling
- B) Preoperative MIBG scan
- C) Open adrenalectomy due to concern for malignancy
- D) Alpha and beta blockade for 3 months
- E) Alpha blockade then laparoscopic adrenalectomy
Question 3: You advise which management:

- A) Bilateral adrenal vein sampling
- B) Preoperative MIBG scan
- C) Open adrenalectomy due to concern for malignancy
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- E) Alpha blockade then laparoscopic adrenalectomy
Pheochromocytoma

Perioperative Management

• $\alpha$ blockade
  – Phenoxybenzamine, Doxazosin
  – Orthostatic hypotension, tachycardia, nasal congestion

• Metyrosine

• $\beta$ blockade
  – Tachycardia, extrasystoles, arrhythmias

• Calcium channel blockers

• Liberal fluid and salt intake
Pheochromocytoma

_Intra-operative Management_

- A line
- CVP
- Nitroprusside, nicardapine, phentolamine
- Esmolol
- Fluid and adrenergic agents
Risk Factors for Hemodynamic Instability during Surgery for Pheochromocytoma

Pretreatment $\alpha$ blockade (PXB or DOX)
48 of 73 (66%) MAP $\leq$ 100 mm Hg
39 of 48 (81%) BP $\leq$ 130/85 mm Hg
25 of 73 (34%) MAP $>100$ mm Hg

Bruynzeel et al JCEM 2010
Risk Factors for Hemodynamic Instability during Surgery for Pheochromocytoma

Intraoperative time SBP above 160 mm Hg plasma norepinephrine levels \( (r = 0.23; P < 0.05) \), tumor diameter \( (r = 0.36; P < 0.01) \), postural BP fall \( (r = 0.30; P < 0.05) \).

Bruynzeel et al JCEM 2010
Risk Factors for Hemodynamic Instability during Surgery for Pheochromocytoma

- Postoperative MAP was significantly higher PXB vs DOX ($P < 0.01$).
- No relation between the PXB or DOX dosage and intraoperative BP fluctuations or postoperative hypotension.
- The doses of esmolol (25 patients) were significantly higher in the PXB group compared with the DOX group (314.5 mg, 25.0–5520; vs. 95.0 mg, 0.06–2500 mg; $P < 0.05$).
- Other vasoactive drugs as phenylephrine (n = 15), nitroglycerine (n = 24), NE (n = 36), and phentolamine (n = 28) did not differ between both groups.

Bruynzeel et al JCEM 2010
Pheochromocytoma

Postoperative Management

• Pathology difficult
• Malignancy
  – Invasion, metastasis
• Annual follow up
  – 16% recurrence at 10 years
    • Malignant
    • Right
    • Extra-adrenal

Amar et al JCEM 2005
Primary Hyperaldosteronism

• Drug resistant hypertension
• Hypokalemia
  – Spontaneous (< 3.5 mEq/L)
  – Severe diuretic induced (<3.0 mEq/L)
• Majority of patients with PA are normokalemic
Primary Hyperaldosteronism

Screening, Confirmation

• HTN

• Aldosterone to Renin Ratio (ARR):
  – PAC (ng/dl) to PRA (ng.ml)
    • ARR > 30 combined with PAC > 20
    • Morning, out of bed 2 hours seated for 15 minutes

• Lack of suppression
  – High salt diet
  – Saline suppression
Primary Hyperaldosteronism

*Imaging and Localization*

- CT imaging
- Young patient, <40, unilateral adenoma, normal contralateral gland = no further imaging
- Older, bilateral abnormal glands, or unilateral microadenoma
  - Bilateral adrenal vein sampling (AVS)

Zeiger et al Endocrine Practice 2009
Primary Hyperaldosteronism

Adrenal Vein Sampling

• Success right vein catheterization survey: 74%, referral center: 95%

• Continuous cosyntropin stimulation

• Corrected aldo/cortisol ratios one side to the other 4:1: unilateral disease

• CTS alone:
  – 21% inappropriate excluded from surgery
  – 25% inappropriate adrenalectomy

Young et al Surgery 2004; Nwariaku Arch Surg 2006
Primary Hyperaldosteronism

Therapy

- Medical: spironolactone, eplerenone
- Unilateral adrenalectomy
  - 100% cure hypokalemia
  - 90% significant improvement in HTN
  - 30-60% cure HTN
- Young, women, shorter duration of HTN, less drugs, normal Cr, no family history of HTN

# Hyperaldosteronism

## Surgical Therapy - Outcome

<table>
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<tr>
<th>Variable</th>
<th>Normal BP</th>
<th>Persistent HTN</th>
<th>P-value</th>
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<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<td>&lt; 40</td>
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<td>&gt; 50</td>
<td>57%</td>
<td>43%</td>
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<tr>
<td>Family Hx HTN</td>
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<td></td>
<td>NS</td>
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<tr>
<td>K</td>
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<td>NS</td>
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<td><strong>Duration HTN (mo)</strong></td>
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</table>

Obara Surgery et al 1992
Case History 2

- 58 year old male had a PET-CTS which shows a 3 cm FDG avid mass in the left adrenal gland. He has a history of melanoma on the left leg and had excision and groin lymph node dissection.
Question 2: The next best course of action is which of the following:

- A) Repeat CTS in 3 months
- B) Proceed to laparoscopic adrenalectomy
- C) 24 hour urine metanephrines
- D) FNA biopsy to determine if it is recurrent melanoma
- E) Open adrenalectomy
Question 2: The next best course of action is which of the following:

- A) Repeat CTS in 3 months
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- C) 24 hour urine metanephrines
- D) FNA biopsy to determine if it is recurrent melanoma
- E) Open adrenalectomy
Adrenocortical Carcinoma

- Determinants of survival
  - Stage at presentation
  - Curative resection
Adrenocortical Carcinoma

Presentation

• Paucity of symptoms
• Abd pressure or mass
• 2/3 hormonally active
  – Cushings
  – Virilization
Adrenocortical Carcinoma

**Imaging**

- Radiographic phenotype
  - < 5% of incidentalomas
  - 2% lesions < 4 cm, 6% 4.1-6 cm
  - 25% > 6 cm
  - > 10 HU on noncontrast CTS (most > 30 HU)
  - < 50% washout on delayed contrast CTS
  - Irregular borders, heterogeneous, metastatic

Barzon et al Eur J Endocrinol 2003; Angeli Horm Res 2000;
Adrenocortical Carcinoma

Biochemical Evaluation

- Detailed hormone evaluation
- Steroid precursors
  - DHEA-S
- Identify tumor marker
Incidentaloma: *Metastatic Disease*

- 2.1-2.5% prevalence of metastatic disease among incidentalomas
- Occult malignancy: adrenal mass at presentation 5.8%
- FNAB: only in patients with history of cancers (particularly lung, breast, kidney),
  - no signs of other metastases,
  - a heterogeneous mass with a high unenhanced attenuation value (>20HU)
  - after exclusion of pheochromocytoma.
- PET CTS

Schteingart et al Endocrine Related Cancer 2005; Barzson et al Eur J Endocrinol 2003; Lee et al Surgery 1998
Adrenocortical Carcinoma

Operative Management

• Open resection
  – En bloc

• Laparoscopy
  – Local and peritoneal dissemination
Adrenocortical Carcinoma
Medical Therapy

• Adjuvant treatment *Controversial*
  – Mitotane (inhibit adrenocortical steroid biosynthesis)
    • Complete resection with poor prognostic features
    • Prolong disease free survival
    • No effect on overall survival
    • Start early
    • Toxicity

Huang and Fojo JCEM 2008; Terzolo et al NEJM 2007
Adrenocortical Carcinoma

Medical Therapy

• Metastatic disease: PET CTS
  – Radiation
    • Symptomatic local recurrence or bone, brain, other mets
  – RFA: option but value is not proven
  – Chemotherapy
    • The evidence regarding efficacy of first-line therapy is very limited (level C). Possible protocols are:
      • Etoposide+doxorubicin+cisplatin+mitotane
      • Streptozotocin+mitotane
      • Mitotane alone or platin+etoposide+mitotane

Schteingart et al Endocrine Related Cancer 2005