Adrenal Tumors:

Evaluation and Management

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When will you find an adrenal tumor?

- During evaluation for suspected adrenal problem
- During staging workup for cancers
- During workup of abdominal (or pulmonary) complaints

Masses found during evaluation for suspected adrenal problem…

- In general, do not image adrenals unless biochemistry indicates underlying hormonal problem
  - Cost, inconvenience
  - Incidentalomas are COMMON

Adrenal hypersecretion syndromes

- Hypercortisolism
- Hyperaldosteronism
- Hyperandrogenism/hyperestrogenism
- Pheochromocytoma

Clinical Features Of Cushing Syndrome (Hypercortisolism)

Obesity	**94%**	**Psychological symptoms**	**40 %**
Facial plethora	**84%**	**Bruising**	**36 %**
Hirsutism	**82 %**	**Congestive heart failure**	**22 %**
Menstrual disorders	**76 %**	**Edema**	**18 %**
Hypertension	**72 %**	**Renal calculi**	**16 %**
Muscular weakness	**58 %**	**Headache**	**14 %**
Back pain	**58 %**	**Polyuria/polydipsia**	**10 %**
Striae	**52 %**	**Hyperpigmentation**	**6 %**
Acne	**40 %**		
		Loss of libido	**~100%**

Diagnosis of Cushing Syndrome: A Complex problem

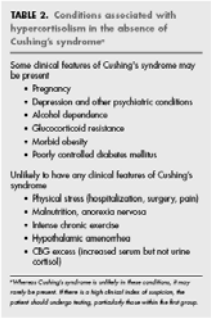


TABLE 2. Conditions associated with hypercortisolism in the absence of Cushing's syndrome*

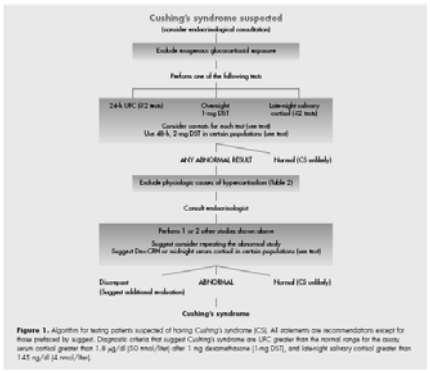
Some clinical features of Cushing's syndrome may be present
- Pregnancy
- Depression and other psychiatric conditions
- Alcohol dependance
- Glucocorticoid resistance
- Morbid obesity
- Poorly controlled diabetes mellitus

Unlikely to have any clinical features of Cushing's syndrome
- Physical stress (hospitalization, surgery, pain)
- Malnutrition, anorexia nervosa
- Intense chronic exercise
- Hypothalamic amenorrhea
- CBG excess (increased serum but not urine cortisol)

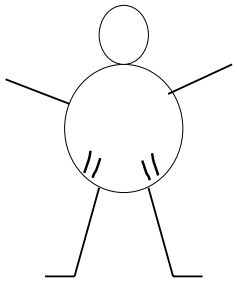
*Whereas Cushing's syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.

From The Endocrine Society's Clinical Guidelines for the Diagnosis of Cushing syndrome (2008)

Current screening guidelines for CS



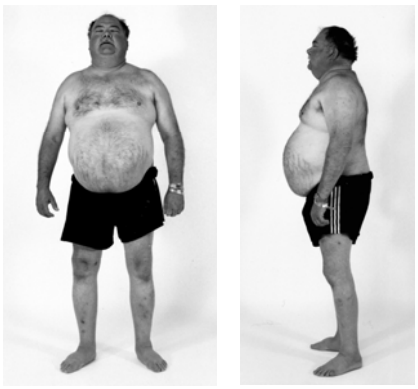
Cortisol hypersecretion:
When to suspect Cushing Syndrome?

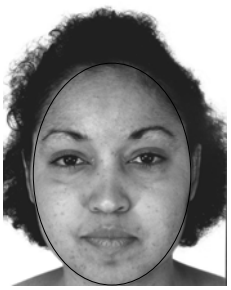


Plethora,
Moon facies

Centripetal obesity, striae

Peripheral muscle wasting

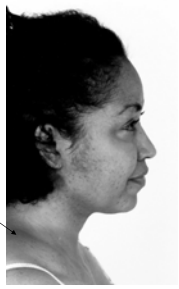




Round face

Acne

Supraclavic fullness



Diagnosis of Cushing Syndrome

- 1 mg Dexamethasone suppression test
- Elevated UFC (24 hr urine free cortisol)
- Loss of diurnal rhythm of cortisol
  - Midnight salivary cortisol
    - 4 pm value with low specificity/sensitivity
- After diagnosis of CS is made, need to determine the source
  - ACTH level (suppressed in adrenal CS)
    - Measurement of ACTH needs to be done properly!

Management of CPAs

- Ensure that this is a primary adrenal issue
  - Nodules can arise in the setting of hyperplasia, but surgery not recommended if ACTH-dependent hyperplasia
- Laparoscopic removal appropriate, unless suspicion for cancer
  - E.g., large mass (>10 cm), irregular or heterogenous characteristics
  - Patients will need peri-operative steroid coverage
  - Recovery of the endogenous adrenal axis may be quite prolonged (1-2), typically longer that pituitary Cushing syndrome

Aldosterone hypersecretion:
When to suspect Hyperaldosteronism?

- Unusual hypertension
- Unexplained hypokalemia

Diagnosis of Primary Hyperaldosteronism

- Screening: Aldo:Renin Ratio (ARR)
  - Primary hyperaldo will have ARR>25, in setting of elevated Aldo
    - Indicates high aldo, low renin state (i.e., renin independent)
- Confirmatory: Saline suppression test
  - 2l NS over 4 hr, measure Aldo every hour
  - Volume expansion should shut down normal Renin-Angiotensin-Aldo axis
  - If primary hyperaldo, serum Aldo will remain elevated

Management of aldosterone-producing adenomas (APAs, Conn adenomas)

- After diagnosis of primary hyperaldosteronism is made, patient should have adrenal vein sampling
  - Problem with incidentaloms
  - APAs can be quite small (unlike CPAs)
- Measurement of aldosterone and cortisol is necessary to ensure proper placement of catheters

Adrenal Vein Sampling
Right-sided adenoma

Pt: JW, 55 yr old man with HTN, low K, small R-sided adenoma on CT

	Pre-ACTH			Post-ACTH		
	Right	Left	Periph	Right	Left	Periph
Aldo	1126.8	19.2	15.6	>1200	611.6	66
F	23.6	24.1	3.4	1009	1735	20.4
A/F	47.75	0.80	4.59	>1	0.35	3.24

Right side elevated
Left side suppressed

Management of aldosterone-producing adenomas (APAs, Conn adenomas)

- Surgery is recommended only if clear unilateral gradient
  - Laparascopic generally preferred
- Otherwise, medical management is suggested
  - Spironolactone, titrate dose to effect
  - Eplerenone
  - If not tolerated, can use “standard” treatments as well

Sex-steroid secreting tumors

- These are fairly uncommon tumors, although typically clinically obvious
- Virilizing tumors
  - Virilization of females
  - Need to rule out ovarian source of hormones
  - May be benign or malignant
- Feminizing tumors tend to be very bad actors in adults (mostly cancers)
  - Feminization of male
  - Can also present as estrogenization of post-menopausal woman
- Management is surgical extirpation (laparoscopic)

Pheochromocytomas

- Symptoms (like for many other endocrine diseases) are often non-specific
- Screening tests:
  - Plasma free metanephrines (NIH)
    - Easier, but more false positive
  - Urinary catecholamines + fract. metanephrines (Mayo)
- In both tests, patients with real disease tend to be *far* above cut-off for normal patients.
  - Patients with slightly elevated values likely do NOT have tumor
  - Medications most common cause for false positive

Pheochromocytomas - II

- Patients with intermediate values may need further evaluation
  - Clonidine suppression test
  - Glucagon stimulation test
- Most clinically evident pheos are easily visualized by imaging
- In general, because of potential hemodynamic alterations, management (surgery) of these tumors best handled in experienced centers
  - Laparoscopy generally with fewer BP swings than open surgery

What to do if suspected hormone hypersecretion is confirmed?

- After verification of biochemistry, THEN perform imaging
- In case of hyperaldosteronism, AVS is recommended
- Other testing (e.g., PET, MIBG) may be helpful if multiple nodules are seen
- Secretory adrenal tumors are usually easily seen (e.g., >2-2.5 cm), with the exception of APAs
- Once tumor is confirmed, surgery is recommended
  - Laparascopic surgery is appropriate for adrenalectomy unless suspicion for malignant disease
    - E.g., large mass (>10 cm), irregular or heterogenous characteristics
  - CPA patients will need peri-operative steroid coverage
    - Recovery of the endogenous glucocorticoid axis may be quite prolonged (1-2), typically longer that pituitary Cushing syndrome

…During staging workup for cancers

- Adrenal incidentaloma most likely to be metastatic disease (75%)
- Adrenalectomy for metastatic cancer of known or unknown primary of unclear benefit

…During workup of abdominal (or pulmonary) complaints

- Adrenal incidentalomas
  - "masses…discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal disease…"
  - "excludes patients undergoing imaging procedures as a part of staging and workup for cancer."
    - NIH consensus statement, August 8, 2002

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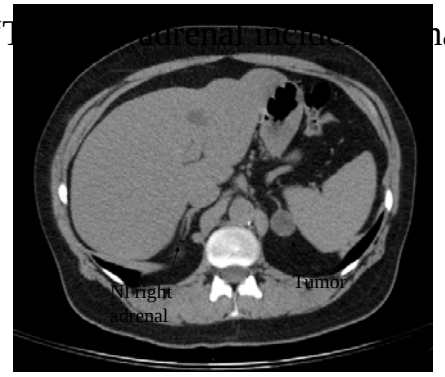


Incidence

- Population and autopsy studies suggest rate of incidentaloma around 5%
  - Patients: F > M
  - Autopsy F = M
- Age dependent
  - <1% at age 30
  - 7% at age 70

Does anything need to be done?

- Indications for intervention
  - Is it hormonally active?
  - Is it cancer?

Screening for sub-clinical hormone secretion

- Hypercortisolism
  - 1 mg O/N dexamethasone suppression test
    - OPD test: 1 mg DEX at 11 pm
    - Draw cortisol level at 8am next day
    - Criteria vary for diagnosis, but normals <2 ug/dL
  - 24 hr Urine free cortisol (UFC) not helpful, since it is usually *not* elevated in sub-clinical cases
  - Nighttime salivary cortisol also of questionable value
  - Plasma ACTH may be helpful in screening stages
    - Should be suppressed if autonomous cortisol secretion, but it is notoriously hard to get accurate results

Screening for sub-clinical hormone secretion

- Hyperaldosteronism
  - Screening only indicated for suspicion of an abnormality
    - Hypertension
    - Unexplained hypokalemia
      - E.g., no diuretics
  - Screen with Aldo/renin ratio (ARR)

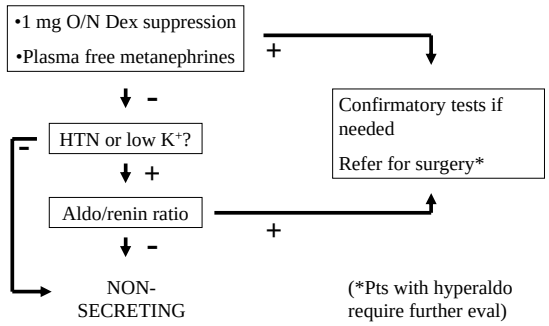
Screening for sub-clinical hormone secretion

- Pheochromocytoma
  - Asymptomatic pheos are not especially unusual
    - 15-20% of incidentalomas resected are pheos
    - Up to 57% of pheochromocytomas resected are detected incidentally
  - Screening either by
    - Plasma free metanephrines (PFM)
    - Fractionated 24 hr urine metanephrines/catechols
      - Plasma catecholamines not usually helpful

Interpreting the tests

- Each test has a very high negative predictive value
  - That is, if tests are normal, mass is almost certainly non-functioning (>95%)
- If testing is abnormal, usually further testing is indicated
  - Remember, these are *screening* tests
    - High sensitivity at the expense of specificity

Hormonal screening of AI's



Is it cancer?

- Adrenal cortical cancer (ACC) is still *very* rare (approx 1 per million)
  - However, metastatic disease not uncommon
- Risk of ACC is size dependent

Size	Likelihood of CA
<4 cm	2%
4-6 cm	6%
>6 cm	25%

NOTE: This is a surgical series, so actual incidence of ACC is lower, because most small, benign-appearing lesions will not get sent for surgery

Imaging of AIs

- Generally, adrenals best visualized on dedicated fine cut CT scan
- Unenhanced CT density <10 HU strongly suggestive of benign process (lipid rich adenoma)
  - Enhanced CT density is NOT helpful
  - Delayed enhanced CT scan can identify lipid-poor adenomas
    - Rapid washout of contrast → benign tumor
  - Phase shift MRI also gives data on lipid content
    - But…anatomy generally not as good
- **Benign masses are typically uniform and round. Other radiological characteristics raise suspicion for malignancy.

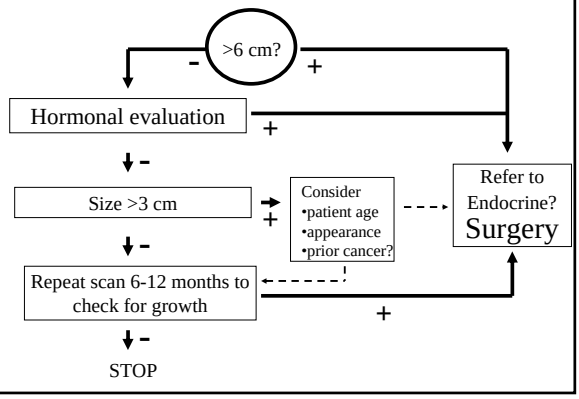
Natural history of AIs

- Little long-term data on these patients
- In limited data, approx 5-25% of lesions will grow at least 1 cm
- Patients that initially do NOT have hormone excess are unlikely to develop it
  - Estimates suggest 20% or fewer will develop

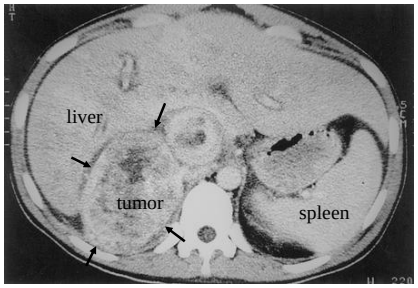
Surgery of AI's

- Most centers now use laparascopic adrenalectomy routinely
  - Requires a skilled surgeon
  - Comparable results, less morbidity
- Contraindicated for strong suspicion of CA
- **Patients with subclinical hypercortisolism should receive peri-operative glucocorticoid coverage

Incidentaloma algorithm



What about those "Bad" adrenal tumors?



Presentation of ACC

- Incidentaloma, often large in size
  - avg size of ACC is ~10 cm
  - Prognosis is poor, due to early metastasis and poor response to therapy
- ~40% of ACC will present as abdominal mass/flank pain (non-secretory)
- Remainder will present as secretory syndrome
  - Tumors often secrete multiple hormones, although these may not be clinically evident

What to do with suspected ACC?

- Generally these patients should be referred
  - Availability of integrated care
    - Endocrinology, Oncology, Surgery, XRT, etc.
  - Participation in clinical trials

Things NOT recommended

- Hormonal studies
  - Random cortisol
  - Plasma catecholamines
  - Isolated aldosterone
- Imaging before biochemistry
- Adrenal biopsy
  - EXCEPT as means to prove metastatic disease

Why not to biopsy the adrenal

- If unsuspected pheo → hypertensive crisis
- If ACC → track metastases
- If ACC → may not able to determine benign from malignant
- If adenoma → cannot determine secretory state
- Requires skilled radiologist

Take home messages

- Most secretory adrenal masses are *obvious* on imaging
  - Aldosteronomas may be an exception
- Most incidentalomas will not require intervention
- Refer patients
  - with suggestive or equivocal hormonal findings
  - For concerns regarding pre-op/peri-op management (cortisol adenomas, pheos)
  - For concern about cancer