Adrenal Update

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HEFT
The adrenal steroidogenesis pathway

- ACTH
  - Cholesterol
    - CYP11A1
    - STAR
  - 17α-hydroxylase CYP17A1
    - 3β-HSD2 HSD3B2
    - 21-hydroxylase CYP21A2
      - Aldosterone synthase CYP11B2
        - Corticosterone
          - 180H-corticosterone
            - Aldosterone
          - 11-deoxycorticosterone
        - Cortisol
          - 17OH-pregnenolone
            - 17α-hydroxylase
              - 17,20-lyase
            - 17α-hydroxylase CYP17A1
              - DHEA
              - Androstenedione
                - Testosterone
      - 11β-hydroxylase CYP11B1
        - Zona glomerulosa Mineralocorticoids
          - Zona fasciculata Glucocorticoids
            - Zona reticularis Androgens
The incidental adrenal mass
Case 1

- 73 yrs. Female.
- Incidental extremely large mass arising in the left retroperitoneum, adrenal rather than renal, para-aortic LNs
- Does not look Cushingoid, BP is well controlled on three medications
- Baseline cortisol 417, Low dose dexamethasone suppression test suppressed to 28 and 24
- x2 urinary cortisol <45 & <35
- ACTH 51 ng/l (7-63)
- Urine metanephrines <23
- A/R ratio (Normal)
- **DHEAS 18.56 umol/l (0.26-6.68)**
- Urine steroid profile: high output of androgens and metabolites and 17 hydroxyprogesterone
- Diagnosis? Management?
Case 2

- 65 yrs. Female
- CA breast with previous mastectomy 2010
- Bilateral incidental adrenal nodules on staging CT, much more noticed on the Lt. 28 mm
- Ald/Renin 57.
- DHEAS 1.06
- Metanephrines <8, <15.
- Management?
Case 3

- 82 yrs. Female
- CT scan: 4.1cm right adrenal mass
- This is of solid attenuation with no evidence of macroscopic fat
- Low dose dex, she did not fully suppress and her lowest cortisol was 89
- ACTH at baseline was 7. DHEAS was undetectable
- Laparoscopic right adrenalectomy March 2012
- Post operative suboptimal synacthen test
Definition ..
Approach..

- A term coined in reference to the phenomenon of detecting an otherwise unsuspected adrenal mass on radiologic imaging
- (1) Is the tumor hormonally active? (2) Does it have radiologic characteristics suggestive of a malignant lesion? (3) Does the patient have a history of a previous malignant lesion?
- The patient should be tested for evidence of hypercortisolism, aldosteronism (if hypertensive), the presence of a pheochromocytoma and androgen secreting tumour.
Age-dependent prevalence of adrenal incidentalomas in five autopsy studies

The Clinical Problem

- 80% a nonfunctioning adenoma
- 5% subclinical Cushing syndrome
- 5% a pheochromocytoma
- 1% an aldosteronoma
- <5% had an adrenocortical CA
- 2.5% had a metastatic lesion
Assessment of Malignant Potential

- Before consideration of surgical resection, a high degree of certainty of the diagnosis is critical.
- The size of the mass and its appearance on imaging are the two major predictors of malignant disease.
- Patient's age and any coexisting conditions.
- Diameter greater than 4 cm have 90% sensitivity for the detection of adrenocortical carcinoma (low specificity; only 24%)
- Size is also important in staging and prediction of prognosis.
Imaging Characteristics
Benign Adenomas

- Round and homogeneous density, smooth contour and sharp margination
- *Diameter less than 4 cm, unilateral location*
- Low unenhanced CT attenuation values (<10 HU)
- Rapid contrast washout
- Isointensity with liver on both T-1 and T-2 weighted MRI sequences
- Chemical shift evidence of lipid on MRI
Imaging Characteristics
Adrenocortical carcinoma

- Irregular shape
- Inhomogeneous density of low attenuation due to tumor necrosis
- Tumor calcification
- Diameter usually >4 cm
- Unilateral location
- High unenhanced CT attenuation values (>20 HU)
- Inhomogeneous enhancement on CT with intravenous contrast
- Delay in contrast medium washout
- Hypo intensity compared with liver on T-1 weighted MRI
- High standardized uptake value (SUV) on FDG-PET-CT study
- Evidence of local invasion or metastases
Hyperaldosteronism
Case 4

- 57 year old F presented with resistant to treat hypertension & CKD
- Verapamil 120 mg twice daily, Moxonidine 300 mcg daily, Doxazocin 8 mg MR twice daily
- Aldosterone 3279 pmol/L(28-445)
- Renin <8
- Saline load test: Aldosterone 1806
- CT : small left adrenal nodule, 2.2cm in diameter
Adrenal Venous sampling

<table>
<thead>
<tr>
<th>Location</th>
<th>Aldosterone</th>
<th>Cortisol</th>
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<tbody>
<tr>
<td>IVC</td>
<td>4620</td>
<td>667</td>
</tr>
<tr>
<td>Rt. Adrenal Vein</td>
<td>5325</td>
<td>3200</td>
</tr>
<tr>
<td>Lt. Adrenal Vein</td>
<td>&gt; 11655</td>
<td>3814</td>
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</table>
Hypertension and hypokalemia
Refractory hypertension
Adrenal incidentaloma
Newly diagnosed hypertension

Plasma renin activity (PRA)
Plasma aldosterone concentration (PAC)

\[ \uparrow \text{PRA} \quad \uparrow \text{PAC} \quad \text{PAC/PRA ratio} \approx 10 \]
Investigate for causes of secondary aldosteronism

Renovascular hypertension
Diuretic use
Renin-secreting tumor
Malignant hypertension
Coarctation of the aorta

\[ \downarrow \text{PRA} \quad \uparrow \text{PAC} (> 15 \text{ ng/dL}) \quad \text{PAC/PRA ratio} > 20 \]
Investigate for primary aldosteronism

Confirm by demonstrating lack of aldosterone suppressibility in the setting of sodium loading
Cushing’s syndrome
Case 5

- 39 year old F, presented with Cushingoid features, obesity, mood disturbance and Type 2 DM
- BMI 41
- Cortisol failed to suppress after overnight and low dose suppression test on 2 occasions
- Raised urinary free cortisol
- Suppressed ACTH
- CT: left adrenal adenoma
- Ketoconazole to control the symptoms
Cushing's syndrome

- Emotional disturbance
- Enlarged sella turcica
- Moon facies
- Osteoporosis
- Cardiac hypertrophy (hypertension)
- Buffalo hump
- Obesity
- Adrenal tumor or hyperplasia
- Thin, wrinkled skin
- Abdominal striae
- Amenorrhea
- Muscle weakness
- Purpura
- Skin ulcers (poor wound healing)
The post-dexamethasone cortisol level provides a measure of autonomous cortisol secretion

Nat. Rev. Endocrinol. doi:10.1038/nrendo.2011.92
The Diagnosis of Cushing’s Syndrome:
An Endocrine Society Clinical Practice Guideline
Medical Therapy

- Metyrapone
- Ketoconazole
- Mitotane (adrenolytic)
- Etomidate
- Other medical agents (octreotide, pasireotide)
- Pasireotide combination therapy with cabergolin and ketoconazole
- Temozolomide
- Retinoic acid
- Thiazolidinedione
- mifepristone
Pheochromocytoma

- 0.01-0.1% of HTN population
- M = F
- 3rd to 5th decades of life
- Rare, investigate only if clinically suspicion:
  - Signs or Symptoms
  - Severe HTN, HTN crisis
  - Refractory HTN (> 3 drugs)
  - HTN present @ young age < 20 or > 50?
  - Adrenal lesion found on imaging (ex. Incidentaloma)
Pheo: Signs & Symptoms

The five P’s:
- Pressure (HTN) 90%
- Pain (Headache) 80%
- Perspiration 71%
- Palpitation 64%
- Pallor 42%
  - Paroxysms (the sixth P!)

The Classical Triad:
- Pain (Headache), Perspiration, Palpitations
- Lack of all 3 virtually excluded diagnosis of pheo in a series of > 21,0000 patients
Pheo: ‘Rule of 10’

- 10% extra-adrenal (closer to 15%)
- 10% occur in children
- 10% familial (closer to 20%)
- 10% bilateral or multiple (more if familial)
- 10% recur (more if extra-adrenal)
- 10% malignant
- 10% discovered incidentally
Familial Pheo

- **MEN 2a**
  - 50% Pheo (usually bilateral), MTC, HPT

- **MEN 2b**
  - 50% Pheo (usually bilatl), MTC, mucosal neuroma, marfanoid habitus

- **Von Hippel-Landau**
  - 50% Pheo (usually bilat), retinoblastoma, cerebellar hemangioma, nephroma, renal/pancreas cysts

- **NF1 (Von Recklinghausen's)**
  - 2% Pheo (50% if NF-1 and HTN)
  - Café-au-lait spots, neurofibroma, optic glioma

- Familial paraganglioma

- Familial pheo & islet cell tumor

- **Other:** Tuberous sclerosis, Sturge-Weber, ataxia-telangectasia, Carney’s Triad (Pheo, Gastric Leiomyoma, Pulm chondroma)
<table>
<thead>
<tr>
<th></th>
<th>SEN</th>
<th>SPEC</th>
</tr>
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<tbody>
<tr>
<td>$U_{\text{catechols}}$</td>
<td>83%</td>
<td>88%</td>
</tr>
<tr>
<td>$U_{\text{total metanephrines}}$</td>
<td>76%</td>
<td>94%</td>
</tr>
<tr>
<td>$U_{\text{catechols+metaneph}}$</td>
<td>90%</td>
<td>98%</td>
</tr>
<tr>
<td>$U_{\text{VMA}}$</td>
<td>63%</td>
<td>94%</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td>85%</td>
<td>80%</td>
</tr>
<tr>
<td>Plasma metanephrines</td>
<td>99%</td>
<td>89%</td>
</tr>
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Localization: Imaging

- CT abdomen
  - Adrenal pheo SEN 93-100%
  - Extra-adrenal pheo SEN 90%

- MRI
  - > SEN than CT for extra-adrenal pheo

- MIBG Scan
  - SEN 77-90%  SPEC 95-100%
Diffuse metastatic pheochromocytoma. 123-I-meta-iodobenzylguanidine scan from a 41-year-old woman shows diffuse metastatic pheochromocytoma. Courtesy of William F Young, Jr, MD.
Pheo Management

Prior to 1951, reported mortality for excision of pheochromocytoma 24 - 50 %
- HTN crisis, arrhythmia, MI, stroke
- Hypotensive shock

Currently, mortality: 0 - 2.7 %
- Preoperative preparation, α-blockade?
- New anesthetic techniques?
  - Anesthetic agents
  - Intraoperative monitoring: arterial line, ECG monitor, CVP line, Swan-Ganz

Experienced & Coordinated team:
- Endocrinologist, Anesthesiologist and Surgeon
Phaeochromocytoma
Preoperative Medical Management

- α-adrenergic blockade for 1 to 3 weeks preoperatively to avoid profoundly unstable intraoperative blood pressure
  
  Phenoxybenzamine, Doxazocin

- Indications for β-adrenergic blockade, which should be given only after adequate α-adrenergic blockade, include persistent tachycardia, extra systoles, or arrhythmias

- Preoperative volume expansion
Hypo-adrenalism

Case 6

- 25 year old M presented with persistent shock despite adequate volume repletion
- Abnormal Lab: hyponatraemia, hypoglycaemia
- History of prolonged steroid use, recent chest infection, Cushinoid appearance
Clinical symptoms at primary diagnosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>96</td>
</tr>
<tr>
<td>Weight loss</td>
<td>73</td>
</tr>
<tr>
<td>Hypotension</td>
<td>72</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>58</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>44</td>
</tr>
<tr>
<td>Salt craving</td>
<td>44</td>
</tr>
<tr>
<td>Loss of pubic and/or axillary hair</td>
<td>36</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>35</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>18</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
</tr>
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</table>

*Results from a patient survey in 113 patients with Addison disease at the Department of Endocrinology, University of Würzburg, Germany.
Skin /mucosal hyperpigmentation is a key sign of primary adrenal insufficiency.
Acute adrenal insufficiency

- Combined glucocorticoid and mineralocorticoid deficiency lead to increased urinary Na loss and hypovolemia
- Inappropriate ADH release and action on the renal tubule due to glucocorticoid deficiency contributes to the hyponatremia
Management of Adrenal Crisis

- Immediate intravenous administration of 100 mg hydrocortisone, followed by 100–200 mg hydrocortisone (in 5% glucose) over 24 h
- Fluid administration, 1,000 ml 0.9% sodium chloride, during the first 60 min
- Further fluid administration guided by central venous pressure
- Monitoring (level 2 or 3 care unit)
Measures for crisis prevention

- Emergency card or bracelet
- Repeated structured education of patient and family
- Discussion of rationale for dose adjustments in stress
- Provision of a hydrocortisone ampule
STEROID TREATMENT CARD

I am a patient on STEROID treatment which must not be stopped suddenly

- If you have been taking this medicine for more than three weeks, the dose should be reduced gradually when you stop taking steroids unless your doctor says otherwise.

- Read the patient information leaflet given with the medicine.

- Always carry this card with you and show it to anyone who treats you (for example a doctor, nurse, pharmacist or dentist). For one year after you stop the treatment, you must mention that you have taken steroids.

- If you become ill, or if you come into contact with anyone who has an infectious disease, consult your doctor promptly. If you have never had chickenpox, you should avoid close contact with people who have chickenpox or shingles. If you do come into contact with chickenpox, see your doctor urgently.

- Make sure that the information on the card is kept up to date.
Emergency card including instructions for steroid emergency administration issued by the United Kingdom Addison's Self-Help Group (ADSHG) (www.addisons.org.uk).

White K, and Arlt W Eur J Endocrinol 2010;162:115-120
Chronic replacement therapy

- Hydrocortisone (15–30 mg daily), treatment surveillance is still primarily dependent on clinical judgment

- Glucocorticoid over-replacement are weight gain, insomnia, peripheral edema

- Under-replacement may be evident by fatigue, weakness, weight loss, nausea, myalgia and joint stiffness
Cortisol Effects: Body Responses to Stress

Circadian rhythm of cortisol secretion
Chronic replacement therapy

- Fludrocortisone is used for mineralocorticoid replacement therapy
- Single oral morning dose of 0.05–0.20 mg
- Measurement of serum sodium and potassium levels, assessment of blood pressure and determination of plasma active renin
Limitations of current replacement regimens

- Circulating epinephrine levels are subnormal in patients with Addison disease.
- Affect glucose availability and limit the maximum capacity for exercise.
- Type 1 diabetes mellitus, extraordinarily vulnerable to exercise-induced hypoglycemia.
- No replacement strategies for epinephrine deficiency are currently available.
Limitations of current replacement regimens

- Nonphysiological components of current treatment regimens
- Impaired well-being with increased fatigue, depression, reduced vitality and increased mortality
- New delayed-release hydrocortisone preparations
CAH
Case 7

- 31 year old F, CAH age 12 years
- On prednislone 5 mgs AM+2.5mgs PM
- BMI 25, BP 112/60
- Feels well, subfertility problem ,Previous IVF trials
- 17OHP (3.5), Rennin( raised )
- Needs help with fertility
The adrenal steroidogenesis pathway

Han, T. S. et al. (2013) Treatment and health outcomes in adults with congenital adrenal hyperplasia
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2013.239
Mutations in the \textit{CYP21A2} gene, which encodes the enzyme 21-hydroxylase

Disrupted cortisol synthesis results in reduced cortisol feedback that increases the release of \textit{ACTH}

Promotes overproduction of (17OHP), progesterone and adrenal androgens

Cortisol deficiency mineralocorticoid deficiency and androgen excess
CAH

- Optimal treatment with glucocorticoids:
  1. 17OHP vary between slightly above the upper limit and thrice the upper limit of the reference range
  2. Concurrent serum levels of androstenedione are maintained within the reference range
- Levels of 17OHP within or below the reference range and a low level of androstenedione are generally thought to indicate excess glucocorticoid exposure
Treating congenital adrenal hyperplasia

Han, T. S. et al. (2013) Treatment and health outcomes in adults with congenital adrenal hyperplasia
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2013.239
A comparison of treatment regimens in relation to biochemical disease control (serum levels of androstendione and 17OHP) and HOMA-IR as an indicator of insulin resistance in the congenital adrenal hyperplasia adult study executive cohort (ANOVA and post hoc analysis)

Han, T. S. et al. (2013) Treatment and health outcomes in adults with congenital adrenal hyperplasia

*Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2013.239
Fertility and pregnancy

- Insufficient glucocorticoid replacement can lead to anovulation and polycystic ovaries in women with CAH.

- Sexual activity in women might be reduced because of poor surgical reconstruction of genital malformations.

- Failure of implantation of a fertilized egg consequent to consistently increased progesterone levels.

- Testicular adrenal rest tissue lead to male subfertility by causing seminiferous tubule blockage resulting in oligospermia or azoospermia.
Any questions?