The Adrenal Glands

The aim of this presentation is to:
1) highlight some of the fundamentals thought in the basic sciences modules to
2) facilitate a better understanding of the strategies adopted in clinical medicine when investigating the functions of the adrenal glands.


NB. If no reference appears on a slide the general reference is *Harrison's Principle of Internal Medicine*. 

2011-11-09   ©lassen-nielsen.com
The Investigations of the Adrenal Glands

Essential for understanding this presentation:

1) **Anatomy:** The Adrenal Glands and their surroundings

2) **Biochemistry:** Hormones produced by the Adrenal Gland

3) **Physiology:** Function of the hormones produced by the Adrenal Gland

First then can one start on a journey to investigate abnormal functions of the Adrenal gland
The Investigations of the Adrenal Glands

Objectives:

1) Describe the mechanisms of endocrine hypofunction and hyperfunction.

2) Differentiate among primary, secondary and tertiary endocrine disorders.

3) Discuss - based on the normal physiology - the rationale behind the investigations of the functions of the Adrenal Glands.
The Investigations of the Adrenal Glands

Essential for understanding the investigations

1) **Anatomy:**

2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**
Question. Can a tumor grow without causing pain?

Yes the gland is embedded in fat that can be ‘pushed’ aside without causing pain?
A rich blood supply is essential for the optimal function of the adrenal glands. Each gland is supplied by the superior, middle and inferior suprarenal arteries, which arise from the inferior phrenic artery, abdominal aorta and renal artery respectively. The blood reaches the outer surface of the gland before entering and supplying each layer. When the blood reaches the adrenal's centre, it flows into the medullary vein. The medullary veins emerge from the hilum of each gland before forming the suprarenal veins, which join the inferior vena cava on the right side and the left renal vein on the left.
Essential anatomy

Note arteries ★★ and veins ★★
Essential anatomy

Which hormones are produced where?
Mineralocorticoids (Aldosterone) in zona glomerulosa
Glucocorticoids (Cortisol) in primarily zona fasciculata
Sex steroids primarily in zona reticularis
Catecholamines in the adrenal medulla
The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
The structure of the steroid hormones:

We have 4 Rings
3 with 6 carbons
1 with 5 carbons
The nomenclature of the steroid hormones:

The rings by capital letters
The carbons by numbers
The nomenclature of the steroid hormones:

Note naming of side chains
The nomenclature of the steroid hormones:

Let’s delete this side chain
Essential biochemistry

The nomenclature of the steroid hormones:

*Let's rearrange a little more*
The nomenclature of the steroid hormones:

What do we have?

Cholesterol

Note we use 17 C’s to build the rings
The total numbers of C’s is used to categorize the steroids hormones
The long process of making the steroid hormones

We start by removing the side chain
Using the ‘Cholesterol side-chain cleavage enzyme’
And we have Pregnenolone
Note we have now 21 C’s
‘Cholesterol side-chain cleavage enzyme’ is the classical name

In 1992 a more systematic database friendly Enzyme Nomenclature was introduced by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB)
A look at the IUBMB nomenclature

Let's take a closer look in the database

Ideally we should now call our enzyme EC 1.14.15.6

It has an unique enzyme number

It gives the names used and the class of enzyme

Note it is a Cytochrome P-450

ENTRY
EC 1.14.15.6
NAME
Cholesterol monooxygenase (side-chain-cleaving)
Cholesterol desmolase
Cytochrome P-450SCC
CLASS
Oxidoreductases

REACTION
Cholesterol + Reduced adenyl ferredoxin + O2 = Pregnenolone + 4-Methylpentanal + Oxidized adrenal ferredoxin + H2O

SUBSTRATE
Cholesterol
Reduced adrenal ferredoxin
O2

PRODUCT
Pregnenolone
4-Methylpentanal
Oxidized adrenal ferredoxin
H2O

COFACTOR
NAD

COMMENT
A heme-cholate protein. The reaction proceeds in three stages, with hydroxylation at C-20 and C-22 preceding scission of the side-chain at C-20.

PATHWAY
PATH: MAPP000140 C21-steroid hormone metabolism

DISEASE
MIM: 118485 Cytochrome P450, subfamily XIA (cholesterol side chain cleavage); Polycystic ovary syndrome with hyperandrogenemia (2)

MOTIF
P2: P003046 F-[RSNH]-x-[CD]-x-[HRHT]-x-C-[ITUMFAAD]-[CAD]

GENES
HSA: CYP11A1(Hs.96295)

STRUCTURES
PDB: 18SO

DDBLINGS
University of Geneva ENZYME DATA BANK: 1.14.15.6
WIT (What Is There) Metabolic Reconstruction: 1.14.15.6
SCOP (Structural Classification of Proteins): 1.14.15.6

DBGET: integrated database retrieval system, GenomeNet
A look at the IUBMB nomenclature

It also gives the reaction, Substrates, products and cofactor

Note it gives the known diseases associated with the enzyme
Naming can be confusing

‘Cholesterol side-chain cleavage enzyme’ is the classical name

In 1992 a more systematic database friendly Enzyme Nomenclature was introduced by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB)

But newer books (i.e. Harrisson’s) uses another code CYP21A1
Naming can be confusing

A 3 minutes hint as to why yet another code is used
http://www.youtube.com/watch?v=983lhh20rGY

But newer books (i.e. Harrisson’s) uses another code CYP21A1
Yes!
The code **CYP21A1** is the **gene symbol** for the gene that codes for the – ‘EC 1.14.15.6 / Cholesterol side-chain cleavage enzyme’

The HUGO Gene Nomenclature Committee is the only worldwide authority that assigns standardized nomenclature to human genes.

The HGNC approves both a short-form abbreviation (**gene symbol**), and also a longer and more descriptive name. Each symbol is unique and the committee ensures that each gene is only given one approved gene symbol. This allows for clear and unambiguous reference to genes, and facilitates electronic data retrieval from databases and publications.  [http://www.genenames.org](http://www.genenames.org)
Aldosterone pathway

Note Aldosterone has 21 C’s
Cortisol pathway

Note alternative pathways exist.

Note Cortisol has 21 C’s.
Sex-steroid pathway

Note the that Testosterone and it’s precursors have 19 C’s

Note Estrone and Estradiol have 18 C’s
The same pathways
Illustration from Harrison’s
The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
Physiology

Higher level stimuli

Negative feed- back

Two loops
CRH → ACTH → feedback to the hypothalamus

ACTH → circulating free Cortisol → feedback to anterior pituitary and hypothalamus
Physiology - cortisol circadian rhythm

Relevant for when you want to test – note peak around 9 o'clock in the morning.

*Figure 342-3 Physiologic cortisol circadian rhythm.*
Remember, aldosterone is controlled by the renin system. Only very little by ACTH.
80 – 90% of circulating Cortisol is bound to **Cortisol Binding Globulin** (CBG) also known as Transcotin. The rest is bound to **albumin** and only a minor fraction circulating as free, unbound hormone. It is believed that it is the free-cortisol that have physiological effect.

So what is the effect of a given dose of cortisol. Since it is protein bound would you start with a large dose or a small dose?

If all CBG and albumin in the blood is saturated with cortisol? The amount you administer will be available as free-cortisol = (be effective)

If CBG and albumin in the blood is not saturated with cortisol? The amount you administer will first be used to saturate the proteins and most of the dose might not be available as free-cortisol = (be effective)

The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
Hyper - & Hypo-functions of glands

In principle only two things can go wrong:

Increased production (over production) of hormones: Hyper......dism

Decreased production (under production) of hormones: Hypo......dism

Of cause there can be many underlying causes: Tumor, starvation, infections .......
A note on nomenclature

**Cushing syndrome** refers to the manifestations of hypercortisolism from **any** cause.

**Cushing disease** refers to hypercortisolism from excessive production of ACTH by the pituitary gland.

Is Cushing disease a primary / secondary or tertiary disease?

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
### Hyper - ACTH

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function (Stimulates)</th>
<th>Releasing factors</th>
<th>Hypo function</th>
<th>Hyper – Function</th>
</tr>
</thead>
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<td>ACTH</td>
<td>Adrenal cortical hormones</td>
<td>CRH</td>
<td>Second. Adrenal hypofunction</td>
<td>Cushing disease</td>
</tr>
<tr>
<td>MSH</td>
<td>Melanocytes</td>
<td>CRH</td>
<td></td>
<td>Skin pigmentation</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid hormone</td>
<td>TRH</td>
<td></td>
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<td>FSH</td>
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<td>GH</td>
<td>Growth</td>
<td>GHRH</td>
<td></td>
<td></td>
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<tr>
<td>PRL</td>
<td>Breast feeding</td>
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<td></td>
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</table>

It is secondary adrenal hyperfunction. **Cushing Disease**

It will be increased production of glucocorticoids from the adrenal gland.

What will be the result of a increased ACTH Production in the pituitary gland?
Glucocorticoid Hormone Excess

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**Figure 342-8 Clinical features of Cushing's syndrome.**

A. Note central obesity and broad, purple stretch marks (B, close-up).
B. Note thin and brittle skin in an elderly patient with Cushing's.
C. Hyperpigmentation of the knuckles in a patient with ectopic ACTH excess.
## Glucocorticoid Hormone Excess - testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Pituitary dependent</th>
<th>Ectopic ACTH</th>
<th>Adrenocortical Carcinoma</th>
<th>Adrenocortical Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cortisol morning</td>
<td>Raised or normal</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised or normal</td>
</tr>
<tr>
<td>Plasma cortisol evening</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
</tr>
<tr>
<td>After low-dose dexamethasone</td>
<td>No suppression</td>
<td>No suppression</td>
<td>No suppression</td>
<td>No suppression</td>
</tr>
<tr>
<td>After high-dose dexamethasone</td>
<td>Suppressed</td>
<td>No suppression</td>
<td>No suppression</td>
<td>No suppression</td>
</tr>
<tr>
<td>Urinary free cortisol</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
</tr>
<tr>
<td>Plasma ACTH</td>
<td>Raised or normal</td>
<td>Raised</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

From Crook, Clinical Chemistry and Metabolic Medicine 2006
Suspected Cushing's Syndrome

Clinical suspicion of Cushing’s
Central adiposity, proximal myopathy, striae, amenorrhea, hirsutism, impaired glucose tolerance, diastolic hypertension and osteoporosis

Screening/confirmation of diagnosis

- 24-h urine free cortisol excretion increased above normal (3x)
- Dexamethasone overnight test (plasma cortisol > 50nmol/L at 8-9 a.m after 1 mg dexamethasone at 11 p.m.)
- Midnight plasma (or salivary) cortisol > 130 nmol/L

If further confirmation is needed/desired:
- Low dose DEX test (plasma cortisol > nmol/L after 0.5 mg dexamethasone q6h for 2 days)

Differential diagnosis 1: Plasma ACTH?
Suspected Cushing's Syndrome

Differential diagnosis 1: Plasma ACTH?

ACTH normal or high > 15pg/ml
ACTH-dependent Cushing’s

ACTH suppressed to < 5pg/ml
ACTH-independent Cushing’s

What is secondary and primary?
Suspected Cushing's Syndrome

ACTH-dependent Cushing's

Differential diagnosis 2:

- MRI pituitary
- CHR test (ACTH increase > 40% at 15-30 min + cortisol increase > 20% at 45-60 min after CHR 100 μg IV)
- High dose DEX test (Cortisol suppression > 50% after q6h 2 mg DEX for 2 days)

CHR test and high dose DEX positive
- Cushing's disease
  - Trans-sphenoidal pituitary surgery Pos
  - Inferior petrosal sinus sampling (petroseal/peripheral ACTH ratio > 2 at baseline, >3 at 2-5 min after CRH 100 μg I.V.)

CHR test and high dose DEX negative
- Ectopic ACTH production
  - Locate and remove ectopic ACTH source Neg
  - Bilateral adrenalectomy Neg

Equivocal results

Suspected Cushing's Syndrome

**ACTH-independent Cushing's**

- Unenhanced CT adrenals
  - Bilateral micronodular or macronodular adrenal hyperplasia
    - Bilateral adrenalectomy
  - Unilateral adrenal mass
    - Unilateral adrenal mass
      - Adrenal tumor work up
    - Unilateral adrenalectomy

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Suspected Cushing's Syndrome

Algorithm for Management of the Patient with Suspected Cushing's Syndrome

Clinical suspicion of Cushing's
(Central adiposity, proximal myopathy, striae, amenorrhea, hirsutism, impaired glucose tolerance, diastolic hypertension, and osteoporosis)

Screening/confirmation of diagnosis
- 24-h urinary free cortisol excretion increased above normal (3x)
- Dexamethasone overnight test (Plasma cortisol >50 nmol/L at 8-9 a.m. after 1 mg dexamethasone at 11 p.m.)
- Midnight plasma (or salivary) cortisol >130 nmol/L
If further confirmation needed/desired:
- Low dose DEX test (Plasma cortisol >50 nmol/L after 0.5 mg dexamethasone q6h for 2 days)

Positive → Negative

Differential diagnosis 1: Plasma ACTH

ACTH normal or high
>15 pg/ml

ACTH-dependent Cushing's

ACTH suppressed to <5 pg/ml

ACTH-independent Cushing's

Differential diagnosis 2

- MRI pituitary
- CRH test (ACTH increase >40% at 15-30 min + cortisol increase >20% at 45-60 min after CRH 100 µg IV)
- High dose DEX test
(Cortisol suppression >50% after q6h 2 mg DEX for 2 days)

CRH test and high dose DEX positive → Equivocal results → CRH test and high dose DEX negative

Cushing's disease → Ectopic ACTH production

Trans-sphenoidal pituitary surgery "Pos."

 Inferior petrosal sinus sampling (petrosal/peripheral ACTH ratio > 2 at baseline, > 3 at 2-5 min after CRH 100 µg i.v.)

Locate and remove ectopic ACTH source → Bilateral adrenalectomy "Pos.", Unilateral adrenalectomy "Neg.", Bilateral adrenal hyperplasia, Adrenal tumor workup

Unenhanced CT adrenals → Bilateral micronodular or macronodular adrenal hyperplasia, Unilateral adrenal mass

Adrenal Gland 43
A. normal

B. bilateral hyperplasia in Cushing's disease

C. right adenoma = Cushing's syndrome

D. Bilateral adenoma = Cushing's syndrome
Glucocorticoid Hormone Excess - testing
The ultimate test: Combining imaging and blood test

50-year-old man with Cushing's disease.

25-year-old woman with Cushing's disease.

**Bilateral inferior petrosal sinuses sampling (BIPSS):** this test may be required to separate pituitary from ectopic causes of ACTH-dependent Cushing's syndrome in patients with a normal pituitary gland on brain MRI scan.

Mineralocorticoid Hormone Excess

A note on nomenclature

**Conn’s syndrome** refers to primary hyperaldosteronism

Symptoms:
Hypertension, hypokalemia and kaliuria
Mineralocorticoid Hormone Excess

Clinical suspicion of mineralocorticoid excess
Severe hypertension (>3 BP drugs, drug-resistant) or Hypokalemia (spontaneous or diuretic-induced) or Adrenal mass or Family history of early-onset hypertension or cerebrovascular events at <40 years of age

Screening
Measurement of aldosterone-renin ratio (ARR) on current blood pressure medication (stop spinrolactone for 4 weeks) and with hypokalemia corrected (AAR screen positive if ARR >750 pmol/L : ng/ml/h and aldosterone > 450 pmol/l) (consider repeat off β-blockers for 2 weeks if results are equivocal)

Rare: Both PRA and aldosterone suppressed

24-h urinary steroid profile (gas-chromatography /mass spectrometry)

Diagnostic for
1) Apparent mineralocorticoid excess (HSD11B2 deficiency), 2) CAH(CYP11B1 or CYP17A1 deficiency), 3) Adrenal tumor-related desoxycorticosterone excess
If negative, consider Liddle’s syndrome (ENaC mutations) (responsive to amiloride trial)
Mineralocorticoid Hormone Excess

Screening

Negative

Confirmation of diagnosis

E.g., saline infusion test (2 litters physiologic saline over 4 h IV), oral sodium loading, fludrocortisone suppression

Unilateral adrenal mass → Unenhanced CT adrenals

Unenhanced CT adrenals → Normal adrenal morphology

Unenhanced CT adrenals → Bilateral micro nodular hyperplasia

Bilateral micro nodular hyperplasia → Family history of early onset art. Hypertension ? Screen for glucocorticoid-remediable aldosteronism

Drug treatment (MR antagonists, amiloride) → Dexamethasone 0.125-05 mg/d
Mineralocorticoid Hormone Excess

Algorithm for the Management of Patients with Suspected Mineralocorticoid Excess

Clinical suspicion of mineralocorticoid excess
Patients with hypertension and
- Severe hypertension (>3 BP drugs, drug-resistant) or
- Hypokalaemia (spontaneous or diuretic-induced) or
- Adrenal mass or
- Family history of early-onset hypertension or cerebrovascular events at <40 years of age

Positive → Negative

Screening
Measurement of aldosterone-renin ratio (ARR) on current blood pressure medication (stop spironolactone for 4 wks) and with hypokalaemia corrected (ARR screen positive if ARR > 750 pmol/L: ng/ml/h and aldosterone > 450 pmol/L) (consider repeat off β-blockers for 2 wks if results are equivocal)

Negative → Positive

Confirmation of diagnosis
E.g., saline infusion test (2 liters physiologic saline over 4 h IV), oral sodium loading, fludrocortisone suppression

Negative → Positive

Unenhanced CT adrenals

Age <40 years (if surgery practical and desired)

- Unilateral adrenal mass
- Bilateral micronodular hyperplasia
- Normal adrenal morphology

Diagnostic for
- Apparent mineralocorticoid excess (HSD11B2 def.)
- CAH (CYP11B1 or CYP17A1 def.)
- Adrenal tumor-related desoxycorticosterone excess
- If negative, consider
  - Liddle's syndrome (ENaC mutations) (responsive to amiloride trial)

PRA and Aldo suppressed → Rared

24-h urinary steroid profile (GC/MS)
Clinical findings of Adrenal insufficiency

Hyperpigmentation:
Skin (bronze tone)
Body creases, nipples,
And mucous membranes

Loss of weight:
Emaciation, anorexia
vomiting, and diarrhea

Cardiac insufficiency, hypotension

Adrenal atrophy, destruction

Urinary losses, sodium, water

Retention of potassium

Hypoglycemia
Poor tolerance to stress, fatigue
muscle weakness

Note:
primary adrenocortical hypofunction = Addison’s disease.
### Hypo - ACTH

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## Clinical findings of Adrenal insufficiency

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<td>Orthostatic hypotension</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Hyponatremia</td>
<td>Yes 85-90%</td>
<td>Yes 60%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Yes 60-65%</td>
<td>No</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Yes &gt;90</td>
<td>No</td>
</tr>
<tr>
<td>Secondary deficiencies of testosterone, GH, thyroxin, ADH</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Associated autoimmune conditions</td>
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From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
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Why is the symptoms at the top the same in both primary and secondary insufficiency?

Why is the symptoms at the bottom different in primary and secondary insufficiency?

What would the symptoms be in tertiary insufficiency?
Clinical findings of Adrenal insufficiency
Suspected Adrenal insufficiency

Clinical suspicion of adrenal insufficiency
Weigh loss, fatigue, postdural hypotension, hyperpigmentation, hyponatremia

Screening / confirmation of diagnosis
Plasma cortisol 30-60 min after 200 μg cosyntropin IM or IV (Cortisol post cosyntropin < 500 nmol/L)
CBC, serum sodium, potassium, creatinine, urea, TSH

Negative

Differential diagnosis
Plasma ACTH, plasma renin, serum aldosterone

Primary adrenal insufficiency
High ACTH, High plasma renin activity, low aldosterone.

Secondary adrenal insufficiency
Low – normal ACTH, normal plasma renin activity, normal aldosterone.
Suspected Adrenal insufficiency

Primary adrenal insufficiency

Glucocorticoid + mineralocorticoid replacement

Positive

Adrenal autoantibodies

Negative

Autoimmune adrenalitis
Autoimmune polyglandular syndrome (APS)

Chest x-ray
Serum 17 OPH
In men: plasma very long fatty acids (VLCFA)
Adrenal CT

Positive

Adrenal infection (tuberculosis)
Infiltrations (lymphoma)
Hemorrhage
Congenital adrenal hyperplasia (17OPH high)

Autoimmune adrenalitis most likely diagnosis
In men, consider adrenoleukodystrophy (MR antagonists, amiloride) (VLCFA high)

Negative
Suspected Adrenal insufficiency

Secondary adrenal insufficiency

Glucocorticoid replacement

MRI pituitary gland

Positive

Hypothalamic-pituitary mass lesion

Negative

• History of exogenous glucocorticoid treatment?
• History of head trauma?
• Consider isolated ACTH deficiency
Clinical findings of Adrenal insufficiency

Algorithm for the management of the patient with suspected adrenal insufficiency

Clinical suspicion of adrenal insufficiency (weight loss, fatigue, postural hypotension, hyperpigmentation, hyponatremia)

Screening/confirmation of diagnosis
- Plasma cortisol 30-60 min after 250 μg cosyntropin IM or IV (Cortisol post-cosyntropin <500 nmol/L)
- CBC, serum sodium, potassium, creatinine, urea, TSH

Differential diagnosis
Plasma ACTH, plasma renin, serum aldosterone

Primary adrenal insufficiency
(High ACTH, High PRA, low aldosterone)
- Glucocorticoid + mineralocorticoid replacement
- Adrenal autoantibodies
  - Positive
  - Autoimmune adrenalitis;
  - Autoimmune polyglandular syndrome (APS)
  - Negative
  - Chest X-ray
  - Serum 170HP
  - In men: plasma very long chain fatty acids (VLCFA)
  - Adrenal CT

Secondary adrenal insufficiency
(Low-normal ACTH, normal PRA, normal aldosterone)
- Glucocorticoid replacement
- MRI Pituitary
  - Positive
  - Hypothalamic-pituitary mass lesion
  - History of exogenous glucocorticoid treatment?
  - History of head trauma?
  - Consider isolated ACTH deficiency
  - Negative

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Figure 342-15. Management of the patient with suspected adrenal insufficiency. PRA, plasma renin activity.
Pheochromocytoma

Pheochromocytomas and paragangliomas are catecholamine producing tumors derived from the sympathetic or parasympathetic nervous system.

Symptoms are variable. Pheochromocytoma has been termed the “the great masquerade”

The classic triad: episodes of palpitations, headaches and profuse sweating accompanied with hypertension makes pheochromocytoma likely.
Pheochromocytoma

- Headaches
- Sweating attacks
- Palpitations and tachycardia
- Hypertension, sustained or paroxysmal
- Anxiety and panic attacks
- Pallor
- Nausea
- Abdominal pain

- Weakness
- Weight loss
- Paradoxical response to antihypertensive drugs
- Polyuria and polydipsia
- Constipation
- Orthostatic hypotension
- Dilated cardiomyopathy
- Erythrocytosis
- Elevated blood sugar
- Hypercalcemia
Pheochromocytoma
## Pheochromocytoma

<table>
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<tr>
<th>Diagnostic method</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td><strong>24 hour urinary tests</strong></td>
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<tr>
<td>Vanillylmandelic acid (VMA)</td>
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<td>++++</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fractional metanephrines</td>
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<td>Total metanephrines</td>
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<tr>
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<tr>
<td>Free metanephrines</td>
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<td>Picture</td>
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<tr>
<td>MIGB scintigraphy</td>
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<td>++</td>
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<tr>
<td>DOPA (dopamine) PET positron emission tomography</td>
<td>+++</td>
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