MEDICINE

432 Team

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Adrenal Disorders

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

1. Anatomy and Physiology of Adrenal Glands.
2. Adrenocortical Insufficiency.
3. Acute Adrenal Crisis.
4. Cushing's Syndrome.
5. Ectopic ACTH Syndrome and Adrenal Tumors.
6. Primary Mineralocorticoid Excess.
7. Pheochromocytoma.

Anatomy and Physiology of Adrenal Glands:

The adult adrenal glands weigh 8-10gm and lie in the **retroperitoneum** above and medial to the upper poles of the kidneys. A fibrous capsule surrounds the gland. The **yellowish outer cortex** comprises 90% of the adrenal weight and the **inner medulla** about 10%.

The outer cortex has three zones:

- *Zona glomerulosa*
- *Zone fasciculata*
- *Zona reticularis*

The inner two zones function as one unit both producing **cortisol** and **androgens,** while *the Zona glomerulosa* produces **mineralocorticoids.**

ACTH "Adrenocorticotropic hormone" regulates the *Zona fasciculata* and *reticularis*. Excess or deficiency of this hormone alters the structure and function of the zones i.e. both zones atrophy when ACTH is deficient and when ACTH is present in excess, hyperplasia and hypertrophy of these zones occur.

The *Zona glomerulosa* produces aldosterone and lacks 17-hydroxylase activities and cannot synthesize cortisol and androgens. The synthesis of aldosterone is primarily regulated by the **renin angiotensin system** and by **potassium level in the blood.**

(Go through the adrenal surgery teamwork for more information)

Regulation of Secretion:

- **Circadian Rhythm:**

Regulates both the magnitude and the number of **CRH "corticotropin-releasing hormone"** and **ACTH** secretory episodes. Cortisol secretion is low in the late evening and high in the early morning.

This rhythm is changed by:

1. Changes in Sleep pattern
2. Light-dark exposure
3. Feeding times
4. Psychological stress
5. CNS and pituitary disorders
6. Cushing syndrome
7. Liver disease
8. Chronic renal failure
9. Alcoholism
10. Certain Drugs e.g. Cyproheptadine

- **Stress:**

Like surgery and hypoglycemia. It causes ACTH and cortisol to be secreted within minutes of the onset of stress and this is mediated by increased CRH secretion. This is abolished by prior high dose glucocorticoid administration and in Cushing's syndrome.

- **Feedback inhibition:**

It occurs by glucocorticoids both at the pituitary and hypothalamus inhibiting CRH and ACTH production and thus further synthesis of glucocorticoids.

Circulation of Cortisol and Adrenal Androgens:

Cortisol and the adrenal androgens circulate bound to plasma proteins. The plasma half-life of cortisol **(70-90 min)** is determined by the extent of plasma binding and by the rate of metabolism.

The hormone after secretion binds to plasma proteins upon entering the circulation. Cortisol binds mainly to **CBG** "**cortisol binding globulin**" or transcortin =75% and to a lesser extent to albumin =15% and **about 10% of circulating cortisol is free and it is this biologically active cortisol which is regulated by ACTH.**

CBG increases in:

1. Pregnancy
2. OCP use
3. Hyperthyroidism
4. Diabetes mellitus
5. Certain hematological disorders
6. Genetic familial conditions

CBG decreases in:

1. Familial deficiency states
2. Hypothyroidism
3. Protein deficiency states
4. Severe liver disease
5. Nephrotic syndrome

Helpful videos:

https://www.youtube.com/watch?v=6HV-awfdRs8

https://www.youtube.com/watch?v=4WJj8IE83oM

Androgens except for testosterone bind weakly to albumin. However, testosterone is bound extensively to a specific globulin – sex hormone binding globulin (SHBG).

Adrenocortical Insufficiency

Primary adrenocortical insufficiency "Addison's Disease"

Definition: Primary adrenal insufficiency, also known as **Addison's disease**, occurs when the adrenal glands cannot produce an adequate amount of hormones despite a normal or increased ACTH level. This is a rare disease, occurring in about 35 to 120 people in every one million people [(1)].

Causes:

Major causes:

Autoimmune = 80%

Tuberculosis = 20%

Rare causes:

Adrenal hemorrhage and infarction
Fungal infections
Metastatic and lymphomatous replacement
Sarcoidosis
Amyloidosis
Hemochromatosis
Radiation therapy
Surgical adrenalectomy
Enzyme inhibitors e.g. Metyrapone
Cytotoxic drugs e.g. Mitotane
Congenital diseases e.g. enzyme defects
Hypoplasia

Idiopathic Addison's disease is frequently accompanied by other glandular failure disorders and also with a higher incidence of other immunological and autoimmune endocrine disorders e.g. hyperthyroidism, hypothyroidism, hashimoto anemia and gonadal failure.

One or more of these disorders is usually present in 40-53% of patients with idiopathic Addison's disease.
Addison's disease is more common in women 2.6:1. It is usually diagnosed in the 3rd to 5th decade.

Clinical features:

The chief symptoms of chronic primary adrenocortical insufficiency are **hyperpigmentation** due to secondary increase in ACTH. **(Very important to differentiate between primary and secondary insufficiency)** This increase is due to a decrease in negative feedback inhibition. Melanocyte-stimulating hormone (MSH) and ACTH are cleaved from the same propeptide, so elevated ACTH results in increased skin pigmentation. It is increased in **sun-exposed areas and accentuated over pressure areas**, palmar creases, nail beds, nipples, areolae, and peri-vaginal and peri- anal mucosae as well as gums and buccal mucosa. Scars formed after the onset of ACTH excess become hyperpigmented.

Weakness, fatigue, anorexia, weight loss → hyperpigmentation → hypotension → G.I disturbances → salt craving "because of sodium wasting secondary to mineralocorticoid deficiency which can also lead to dehydration, hyponatremia, hyperkalemia, and acidosis" → **postural symptoms**

Amenorrhea is common and can be due to weight loss and chronic illness or associated ovarian failure. Loss of body hair can occur secondary to deficient adrenal androgens secretion.

Pathophysiology:

Gradual adrenocortical destruction causes decrease adrenal reserve with normal basal steroid secretion in the initial phase but failure to respond to stress.

Acute crises can be precipitated by stresses of surgery, trauma or infection, which require increased corticosteroid secretion.

With further loss of cortical tissue, even basal secretion of mineralocorticoids and glucocorticoids become deficient leading to the **manifestation of chronic adrenocortical insufficiency** when more than **90%** of both adrenal cortices occur. About 25% of cases present with a **crises or an impending one at the time of diagnosis**

Laboratory findings:

- **Hyponatremia** and **hyperkalemia** are classical in primary adrenal insufficiency.
- There might be **normocytic anemia, neutropenia, eosinophilia** and relative lymphocytosis.
- **Azotemia** and **increased serum creatinine** is due to volume depletion and dehydration.
- **Mild acidosis** is frequently present.
- **Mild to moderate hypercalcemia**

Abdominal radiograph reveal adrenal calcification in half the patients with tuberculosis adrenilitis and in some patients with other invasive or hemorrhagic causes of adrenal insufficiency.

Diagnostic tests:

Since basal levels of adrenocortical steroids may be normal in partial adrenal insufficiency, **test of adrenocortical reserves** are necessary to establish the diagnosis.

Rapid ACTH stimulation test: Cortrosyn test

After a baseline cortisol sample is obtained a synthetic ACTH called **Tetracosactrin** is given in a dose of 0.25mg IM. or IV. and additional cortisol samples are obtained at 30 and 60 min following the injection. **(Peak cortisol levels < 18-20 µg/dl (low i.e. ineffective stimulation) suggests adrenal insufficiency)**

Plasma ACTH levels:

It differentiates between primary and secondary states, being high in the primary form and low normal or low in secondary forms.

Treatment:

Patients with Addison's disease require life long therapy usually with both glucocorticoids and mineralocorticoids.

Hydrocortisone is the preparation used in a dose of 25-30 mg/d. It is usually given as twice per day but can be given once daily or three times daily as suitable for the well-being and normal energy level for each patient.

Fludrocortisone is the mineralocorticoid of choice given in 0.05-0.1 mg/day dose in the morning. In secondary hypoadrenalism fludrocortisone is rarely required.

Secondary adrenocortical insufficiency

The commonest cause of ACTH deficiency is **exogenous glucocorticoid administration.**

Pituitary/hypothalamic tumors are the most common causes of **naturally occurring pituitary ACTH hyposecretion.**

ACTH deficiency is the primary event and leads to decrease cortisol and adrenal androgen secretion. Aldosterone secretion remains normal except in few cases.

The clinical features may be non-specific initially unless acute crises occur in an undiagnosed patient.

Hyperpigmentation is absent because of deficient ACTH and the mineralocorticoid secretion is usually normal. Otherwise the symptoms may be similar to primary electrolytes abnormalities are usually absent and hypotension is usually not present except in acute presentations.

Hyponatremia may occur because of water retention and inability to excrete a water load with no hyperkalemia. **Hypoglycemia** is occasionally the presenting feature.

Acute Adrenal Crisis

What is acute adrenal crisis?

It is a state of acute adrenocortical insufficiency occurring in patients with Addison's disease who are exposed to **the stress of infection, trauma, surgery, hemorrhage or dehydration.**

How do they present?

They present with:

- **Hypotension and shock "may rapidly lead to death"**
- **Fever**
- **Confusion**
- **Dehydration, hyponatremia, hyperkalemia and volume depletion**
- **Weakness, apathy, and depressed mentation**
- **Nausea, vomiting, anorexia**
- **Abdominal pain**
- **Hypoglycemia**

How we could treat them?

1. Parenteral cortisol: commonly used and it has sufficient mineralocorticoid activity so additional treatment is not required.

2. Intravenous fluids: including glucose and saline to correct volume depletion, hypotension and hypoglycemia as well as the acidosis and hyperkalemia, but the shock may not respond to vasopressors unless glucocorticoids are administered.

Adrenal crisis can be prevented in an already diagnosed patient by proper education on dosage of drugs during illness.

Case:

An 18 year old man with hemophilia A who was recently mugged (receiving multiple blows to the back and abdomen) is now complaining of dizziness, abdominal pain, dark patches on his elbows and knees, and uncontrollable cravings for pizza and French fries.
Think: primary adrenal hyperplasia
Next step: ACTH stimulation test

Cushing's Syndrome

Definition:

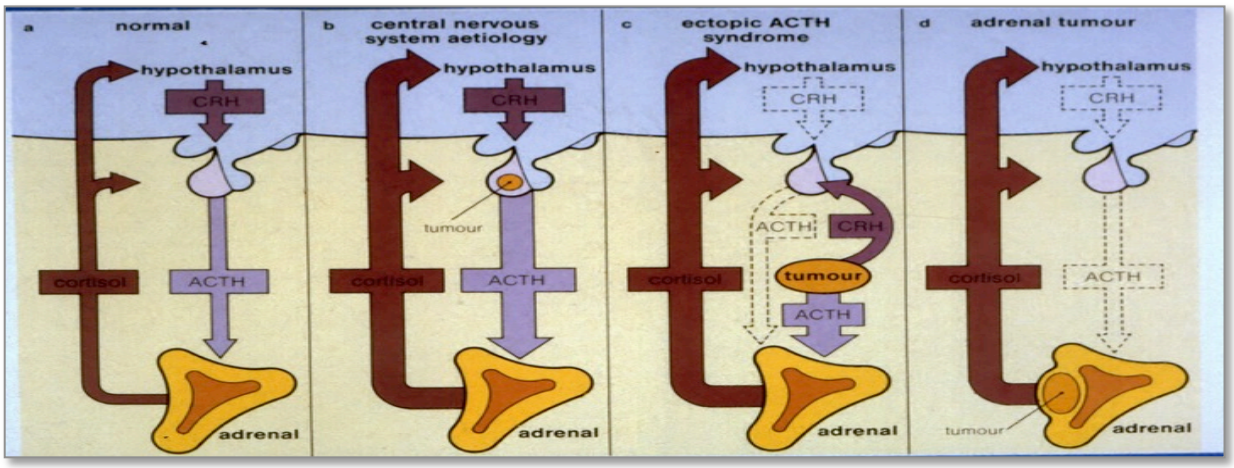
Cushing's syndrome is caused by excessive activation of glucocorticoids receptors. It is most commonly iatrogenic, due to prolonged administration of synthetic glucocorticoids such as prednisolone. Endogenous Cushing's syndrome is uncommon but is due to chronic over-production of cortisol by the adrenal glands, either as the result of an adrenal tumor or because of excessive production of ACTH by a pituitary tumor (Cushing's disease) or ectopic ACTH production by other tumors [(2)].

Causes:

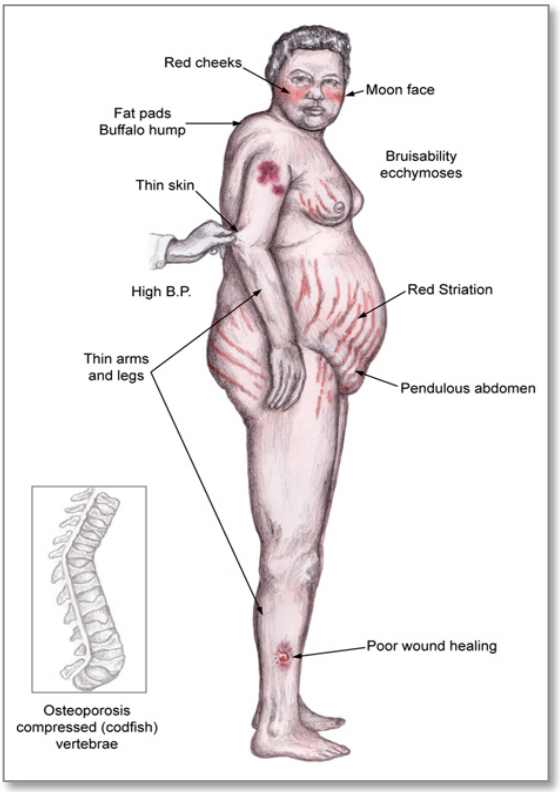
- Iatrogenic

- Adrenal and pituitary tumors: Glucocorticoid producing adrenal adenomas and carcinomas **arise spontaneously** and they are **autonomous** and **not under pituitary hypothalamic control.**

- Ectopic ACTH syndrome, non-pituitary tumors secrete biologically active ACTH. It is more common in men; female to male ratio is 1:3 with the peak incidence at the age of 40-60 years. It is most common with oat-cell carcinoma of the lung (50% of the cases) but other tumors, e.g. pancreatic cell tumors, carcinoid tumors, etc. can cause it.



Clinical features:



http://thehealthscience.com/thsattachs/930938/111918094386219.jpg

1. Obesity: **the most common manifestation,** and is classically central affecting the face **"moonface",** neck, trunk, and abdomen with sparing of the extremities.

2. Skin changes: thinning of the skin because of atrophy of the epidermis and underlying connective tissue. **Striae,** **which are classically red to purple,** are due to loss of connective tissue support as well as **easy bruising.** **Minor wound heal slowly,** and they have frequent mucocutaneous fungal infections. **Hyperpigmentation** is common in Cushing's disease.

3. Hirsutism:

Facial hirsutism is common but it can occur anywhere in the body. It is due to the hypersecretion of adrenal androgens. **Acne and seborrhea** usually present. Virilism occurs in adrenal carcinoma.

4. Hypertension

5. Gonadal dysfunction: **it is very common** as a result of elevated androgens and cortisol e.g. amenorrhea, infertility, and decreased libido.

6. Psychological disturbances: ranges from irritability to anxiety, depression, poor memory and concentration to euphoria and mania as well as sleep disorders. Psychosis and hallucination can occur.

7. Muscle weakness: **commonly proximal and more prominent in the lower limbs.** **(hypokalemia)**

8. Osteoporosis: presenting with **back pain and pathological fractures,** which could occur in severe cases. **(Proteolysis and increased catabolism in general)**

9. Renal calculi: secondary to hypercalcuia.

10. Thirst and polyuria: secondary to development of diabetes mellitus. Asymptomatic glucose intolerance is much more common.

Laboratory findings:

1. High normal hemoglobin and hematocrit are usual with lymphocytopenia and depressed eosinophils count.

2. Hypokalemia alkalosis: may occur in the setting of ectopic ACTH production.

3. Hyperinsulinism and abnormal glucose tolerance tests.

4. High cortisol level: random and episodic with **loss of normal circadian rhythm,** therefore plasma cortisol and ACTH remain elevated throughout the day.

Diagnostic tests:

1. 24-hour urinary free cortisol level.

2. Dexamethasone suppression test:

- It establishes the presence of Cushing's syndrome regardless of the cause.
- It assesses feedback inhibition of the hypothalamic pituitary axis, which is abnormal in Cushing's syndrome.
- For more information check: Medscape, WebMD, YouTube.

3. Radiological studies:

- CT scanning will help in localizing pituitary and adrenal tumors and sometimes, ectopic ACTH production.
- Small tumors may be difficult to detect and selective venous sampling may be needed.

Note(s):

Screening test for clinically suspect patients include the 24-hour urinary free cortisol level and the overnight dexamethasone suppression test.

1: 24-hour urinary free cortisol level should be done twice and be three times higher than norma for confirmation.

2: Dexamethasone suppression tests:

I: Overnight dexamethasone suppression test: 1 mg given at midnight, serum cortisol measured at 8 AM. If <2 µg/100ml, excludes Cushing's as a diagnosis (hypothalamico-pituitary adrenal axis is intact)

II: High-dose dexamethasone suppression test:

8 mg at midnight, serum cortisol measured at 8 AM:

I: ACTH is undetectable or decreased with no cortisol suppression → likely adrenal etiology.

II: ACTH is normal or increased and there's no cortisol suppression → likely ectopic ACTH etiology.

III: ACTH is high with partial cortisol suppression → likely pituitary etiology.

Please make sure that u understand the concepts of hypothalamico-pituitary adrenal axis and negative feedback or these findings will not make much sense to you.

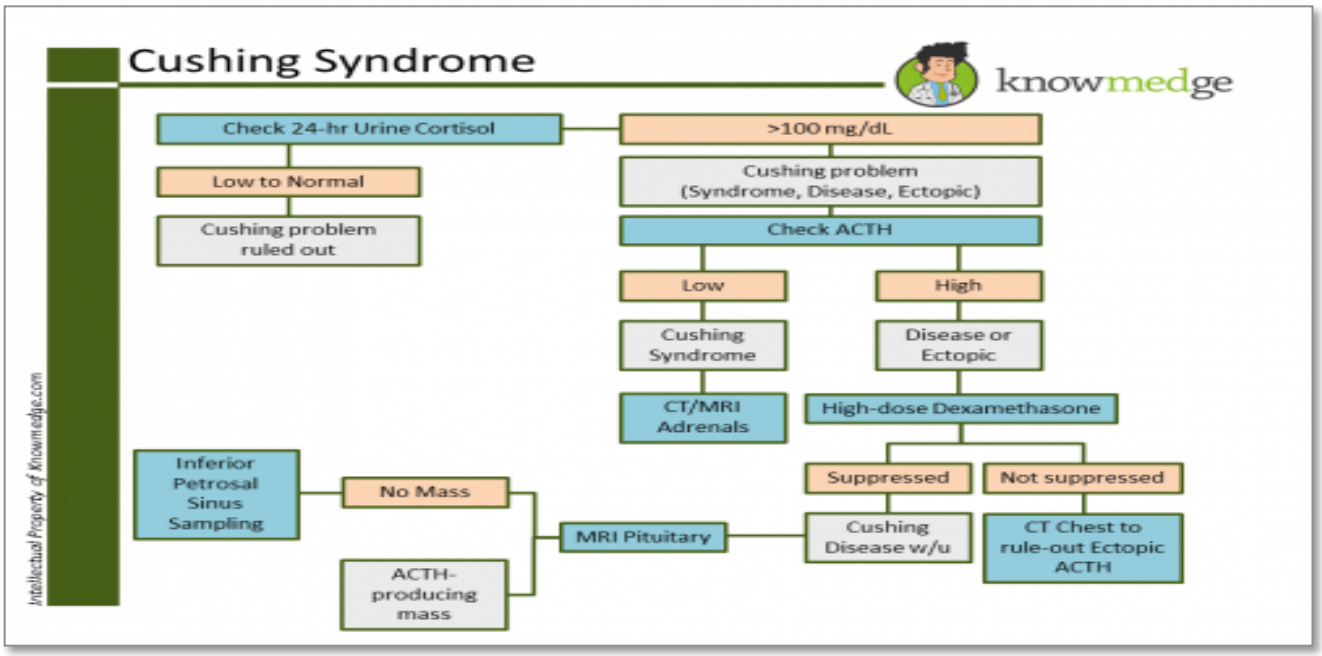
- In some cases, more detailed isotope scanning and arteriography or venography may be needed.

Note(s):

- In Cushing's disease, ACTH is abnormal or modestly elevated while in ectopic syndrome it is markedly elevated.
- In adrenal tumors, ACTH is undetectable.
- The screening test is low dose overnight dexamethasone suppression test, if it was positive despite false positive results then the diagnosis should be confirmed by other tests.
- Cushing's syndrome is confirmed by using two of three main tests:
1. Failure to suppress serum cortisol with low doses of oral dexamethasone.
2. Loss of normal circadian rhythm of cortisol, with inappropriately elevated late-night serum or salivary cortisol.
3. Increased 24-hour urine free cortisol [(2)].

Treatment: is directed at control the ACTH hypersecretion by the pituitary, by the following methods:

1. Microsurgery
2. Radiotherapy
3. Pharmacological inhibition of ACTH secretion



http://knowmedge.com/blog/wp-content/uploads/2014/04/Cushings-e1397451528716.png

Ectopic ACTH Syndrome and Adrenal Tumors

Ectopic ACTH Syndrome

The therapy is directed at removal of the tumor, which **is only successful in the benign tumors,** otherwise drugs that block steroid synthesis can be used e.g. Metyrapone and Mitotane with steroid replacement if necessary.

Adrenal Tumors

Adenomas are successfully treated by adrenalectomy while this treatment for carcinoma is usually unsuccessful and medical therapy can control hypercortisolism in these patients.

Case:

A 42 year old asthmatic woman on long-term steroids has excess adipose tissue in her neck and upper trunk, a wide moon face, and very fine hair.
Think: Cushing's syndrome due to exogenous use

Primary Mineralocorticoid Excess

The increased production of aldosterone by abnormal *Zona glomerulosa* tissue leads to:

- **Increased sodium retention.**
- **Expansion of the total extracellular fluid volume.**
- **Suppression of renin production due to increased total body sodium level.**
- **Potassium depletion leading to alkalosis.**
- **Decreased carbohydrate tolerance and resistance to antidiuretic hormone.**

Causes:

1. **Aldosterone producing adenoma (APA)**
2. **Bilateral adrenal hyperplasia**
3. Indeterminate hyperaldosteronism
4. Dexamethasone suppressible hyperaldosteronism
5. Adrenocortical carcinoma

There are no abnormalities in cortisol production, plasma cortisol levels or cortisol metabolism.

Clinical features:

- ✓ **Symptoms of hypokalemia or detection of previously unsuspected hypertension.**
- ✓ **Non-specific symptoms: tiredness, lethargy, weakness, nocturia, and symptoms of potassium depletion.**
- ✓ **Thirst, polyuria, and paraesthesia due to alkalosis caused by sever hypokalemia** "A positive trousseau or chevostek sign may suggest alkalosis with severe potassium depletion. The ECG shows signs of modest LVH and potassium depletion".
- ✓ **Headache**
- ✓ **Borderline to severe hypertension**

Laboratory findings:

1. **High serum sodium with reduced hematocrit value, due to increased extracellular fluid volume from sodium retention.**
2. **Failure to concentrate urine**
3. **Abnormal glucose tolerance**
4. **Alkalosis**
5. **Hypokalemia**
6. Assess the renin angiotensin system by doing a random plasma renin activity level, if normal or high in the absence of diuretics, then primary aldosteronism is unlikely. If it is suppressed, then primary aldosteronism is the likely diagnosis"*(can be confirmed by a plasma aldosterone to plasma renin activity ratio of more than 20)*

Measurement of aldosterone and other steroids:

Aldosterone measurement **"both plasma and urinary"** should be performed while the patient is taking a high salt diet with sodium chloride supplementation.

Assessment of aldosterone production can be best done by measurement of **urinary aldosterone excretion over 24 hour period** and it is superior to plasma aldosterone measurement in detecting abnormal production of aldosterone, but cannot discriminate between adenoma and hyperplasia. While the plasma levels can differentiate between the two conditions in most cases.

Radiological tests:

1. Scanning using I.V. administered 1^3 iodocholesterol locates tumor in 80% of the cases depending on the size of the tumor.
2. CT scan
3. Adrenal venography

Treatment:

Unilateral adrenalectomy is recommended with adequate potassium replacement, extracellular volume expansion, and control of blood pressure before surgery all of which can be achieved by spironolactone.

In hyperplasia, antihypertensive medication should be given as surgery will not ameliorate the hypertension.

Remember:

Secondary causes of hypertension:
Renovascular hypertension
Primary aldosteronism
Pheochromocytoma
Cushing's syndrome
Renal disease
Acromegaly

Case:

A 44 year old woman has hypertension, muscle cramps and excessive thirst.
Think: Hyperaldosteronism.

Pheochromocytoma

Definition: Pheochromocytomas are tumors arising from **the chromaffin cells in the sympathetic nervous system.** They release epinephrine or norepinephrine "or both" and sometimes dopamine into the circulation causing **hypertension** and other signs and symptom.

They may occur alone or in combination with other endocrine tumors like **MEN type IIA – hyperparathyroidism, pheochromocytoma and medullary thyroid carcinoma**

or **MEN type II B – pheochromocytoma, medullary thyroid carcinoma with mucosal neuroma.**

The Rule of 10s:

- ✓ 10% bilateral
- ✓ 10% Familial
- ✓ 10% Malignant
- ✓ 10% Extra adrenal
- ✓ *10% Pediatric*
- ✓ *10% Calcify*
- ✓ *10% Recur after resection*

Clinical features [2]:

- **Hypertension (usually paroxysmal; often postural drop of blood pressure).**
- **Paroxysms of: pallor (occasionally flushing), palpitations, sweating, headache, and anxiety.**
- **Abdominal pain and vomiting**
- **Constipation**
- **Weight loss**
- **Glucose intolerance**

The 5Hs:

Headache
Hypertension
Heat (diaphoresis)
Heart (palpitations)
Hyperhidrosis

They are usually precipitated by activities that compress the tumor, e.g. change in position, exercise lifting, defecation or eating and by emotional distress or anxiety.

The blood pressure typically does not respond to the common antihypertensive medications. Patients with persistent symptoms and hypertension may develop hypertensive retinopathy or nephropathy.

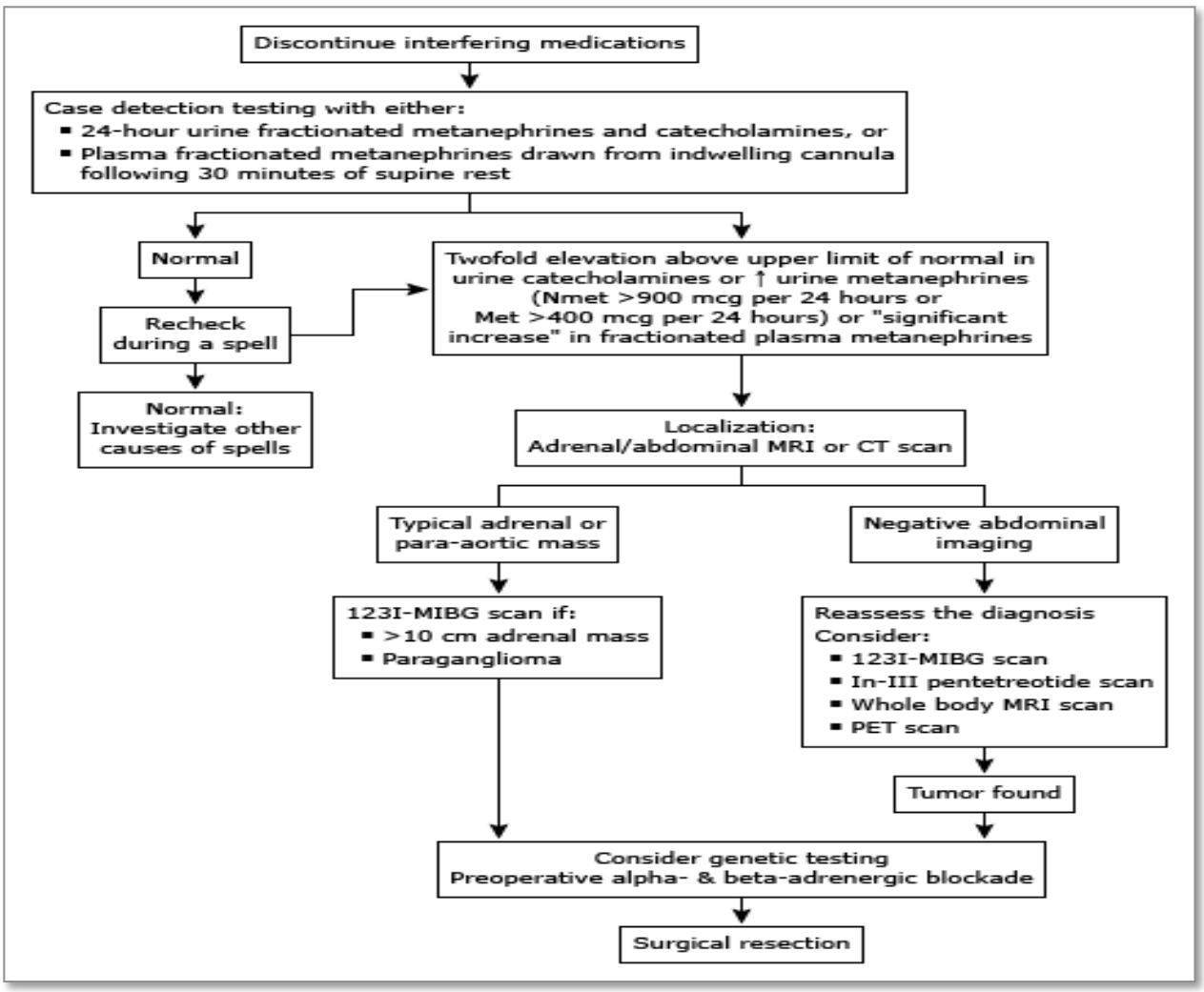
Differential diagnosis:

- Angina due to coronary vasospasm
- Sever anxiety state
- Hypertension
- Hypertensive crisis
- Menopausal hot flushes
- Thyrotoxicosis

We should suspect pheochromocytoma in the following patients:

1. Patients with paroxysmal symptoms.
2. Children with hypertension.
3. Adults with sever hypertension not responding to medications.
4. Hypertensive patients with diabetes or hypermetabolism.
5. Patients who become severely hypertensive or go into shock during anesthesia, surgery, or obstetric delivery.
6. Patients who have disorders sometimes associated with pheochromocytoma e.g. neurofibromatosis, or medullary carcinoma.

Laboratory findings and radiological investigations:



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Treatment: alpha-adrenergic antagonists like phentolamine and phenoxybenzamine; they will allow expansion of the vascular bed and plasma volume. Small doses of propranolol maybe required for marked tachycardia or arrhythmia prior or during surgery.

SUMMARY

1. A table summarizing different features of Addison's disease and Cushing syndrome follows.
2. Primary adrenal insufficiency is due to a problem with the adrenal glands itself.
3. In Secondary adrenal insufficiency the pituitary gland doesn't produce ACTH so that there's no stimulus for the adrenals
4. Tertiary insufficiency is due to hypothalamic dysfunction.
5. Causes of Cushing's syndrome are in order of occurrence:
    a. Iatrogenic
    b. Pituitary tumor
    c. Adrenal adenoma
    d. Ectopic ACTH production

Addison's Disease	Cushing's syndrome
Cortisol deficiency	Cortisol excess
Patient is thin	Patient is obese
Hyponatremia	Hypernatremia
Hyperkalemia	Hypokalemia
Metabolic acidosis	Metabolic alkalosis
Hypotension	Hypertension
Hypoglycemia	Hyperglycemia
Lymphocytosis	Lymphopenia
Eosinophilia	No eosinophilia

IMPORTANT NOTES FROM EXTERNAL RESOURCES

	Notes
(1)	http://www.uptodate.com/contents/adrenal-insufficiency-addisons-disease-beyond-the-basics
(2)	Davidson's Principles and Practice of Medicine 22nd Edition, Endocrine Disease Chapter

The Lecture is too long and there are a lot of diseases so I preferred not to add approach here…..

Questions

1- A 40-year-old alcoholic male is being treated for tuberculosis, but he has not been compliant with his medications. He complains of increasing weakness and fatigue. He appears to have lost weight, and his blood pressure is 80/50 mmHg. There is increased pigmentation over the elbows. Cardiac exam is normal. Which of the following is the best next step in evaluation?

a. CBC with iron and iron-binding capacity
b. Erythrocyte sedimentation rate
c. Early morning serum cortisol and cosyntropin stimulation
d. Blood cultures

2- A 47-year-old male homeless man presents to the indigent clinic. He was recently discharged from the hospital with a diagnosis of Addison's disease (primary adrenal insufficiency). The patient states that the doctor at the hospital told him if he did not take medication he might die. He reports that he left his prescriptions and discharge instructions on the bus that took him to a shelter near the hospital. He asks you to give him new prescriptions. You get his medical records faxed over from the hospital and, after reviewing them, agree with his diagnosis of Addison's disease. Which of the following is the treatment of choice for this patient?

a. Hydrocortisone once per day
b. Hydrocortisone twice per day plus fludrocortisone
c. Hydrocortisone only during periods of stress
d. Daily ACTH

432 Medicine Team Leaders

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For mistakes or feedback: *medicine341@gmail.com*

Answers:

1st Question: C

2nd Question: B