Team Medicine

14#
Adrenal disorders

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431 Teams

Adrenal gland – anatomy and physiology :

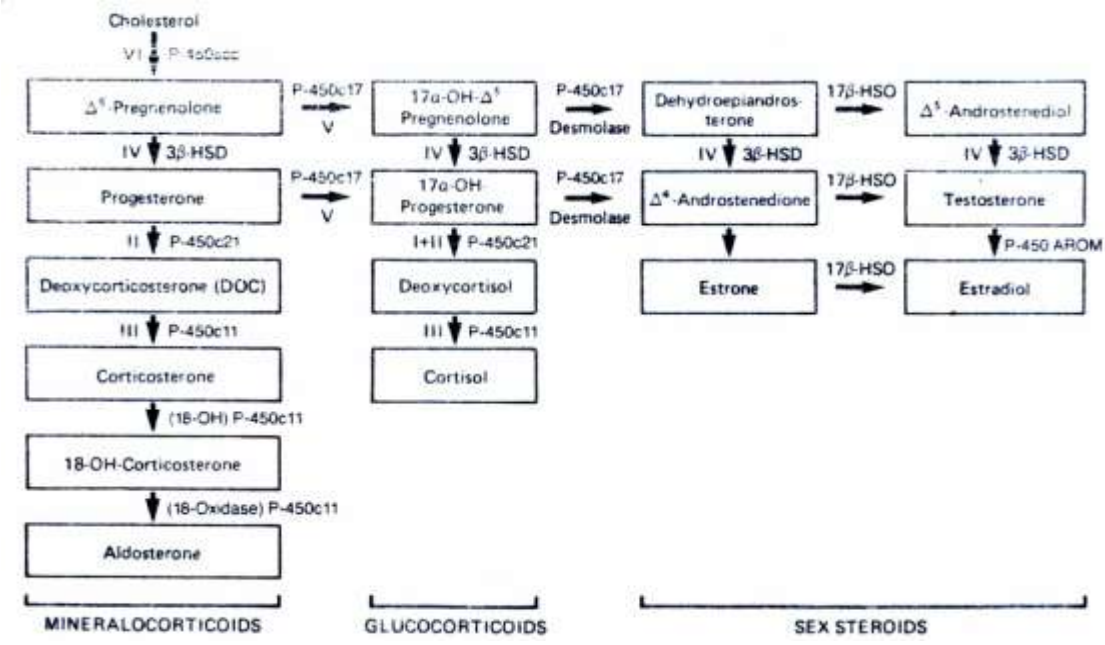
The adult adrenal glands weighs 8-10gm and lie in the retroperitonium (it is very important to remember that it is retroperitonium structure from clinical point of view) above and medial to the upper poles of the kidneys. A fibrous capsule surrounds the gland. The yellowish outer cortex comprises 90% of the adrenal weight and the inner medulla about 10%.

The outer cortex has three zones: (each zone done something different but some time they combine to help each other)

Zona glomerulosa (produce mainly mineralocorticoid)

Zone fasiculata
Zona reticularis
} *The two zones mainly function as one unit*, both producing cortisol and androgens

The zona fasiculata and reticularis are regulated by ACTH .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



what we have to remember from this slide
1-(all adrenal hormone biosynthesis start with cholesterol very complicated pathway)
2-That zona glomerulosa lacks enzyme 17 hydroxylase activity which control synthesize pathway of cortisol and androgens that's why it only produce mineralocorticoid)
3-The synthesis of aldosterone is primarily regulated by the

renin angiotensin system and by potassium.

4- The zona fasciculata and reticularis produce cortisol, androgens and small amounts of estrogens and they do not contain the enzymatic system necessary for production of aldosterone

Regulation of Secretion:

1-Circadian Rhythm

Regulates both the magnitude and the number of CRH and ACTH secretory episodes. Cortisol secretion is low in the late evening and high in the early morning.(afternoon lower than morning)

This rythum is changed by:

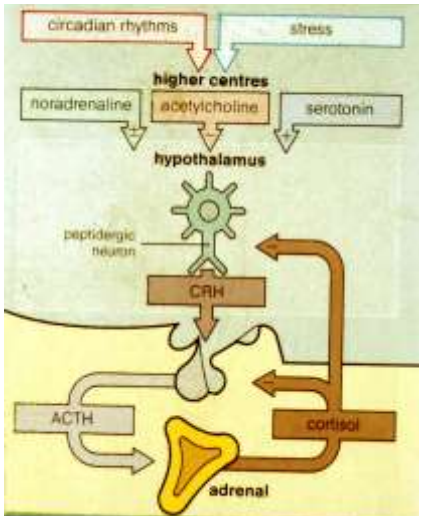
1. Changes in Sleep pattern
2. Light-dark exposure
3. Feeding times
4. Psychological stress
5. CNS and pituitary disorders
6. Cushing syndrome
7. Liver disease
8. Chronic renal failure
9. Alcoholism
10. Certain Drugs e.g. cyproheptadine

2-Stress

e.g. 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.

3-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 & 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 metabolic in activation.

The hormone after secretion bind 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: (doctor said don't worry about the causes that increase and decrease the binding)

1. Pregnancy
2. OCP users
3. Hyperthyroidism
4. D.M.
5. Certain hematological disorders
6. Genetic familial condition

CBG decreases in:

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

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

Disorders of Adrenocortical Insufficiency

Primary adenocortical insufficiency
(Addison's disease(the auto immune part):

Causes

Major Causes

Autoimmune(Addison's disease) = 80%
Tuberculosis = 20%

Rare Causes (so many causes can affect this gland because it is very vascular and tiny structure so any pathology can affect it)

- 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

Idiopathis 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. (diabetes , SlE)

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 diagonsed in the 3rd to 5th decade.

Pathophysiology & clinical features

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

The chief symptoms of chronic primary adrenocortical insufficieny are hyper-pigmentation due to secondary increase in ACTH and BLPH because of decrease negative feedback inhibition
weakness and fatigue, weight loss anorexia, and gastrointestinal disturbances.

Symptom	Percent
Weakness, fatigue, anorexia, weight loss	100%
Hyperpigmentation	92%
Hypotension	88%
G.I. disturbances	56%
Salt craving	19%
Postural symptoms	12%

The generalized hyperpigmentation of the skin and mucous memberanes is the earliest manifestation and 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.
(Some time people use scar as diagnostic test to when did it start ,scars that form after the episode of hypoadrenalism will be pigmented while old scar wont be pigmented)

General weakness, fatigue, malaise, anorexia and weight loss are invariable features.
(cortisol and thyroxin are life saving hormone we cant sustain life without them)
Gastrointestinal disturbances especially nausea and vomiting occur in most patients. Diarrhoea, is less frequent. Hypotension is present in about 90% of

patients and causes orthostatic symptoms. It can cause syncope and in severe cases shock.

Salt craving occurs because of sodium wasting secondary to mineralocorticoid deficiency which can also lead to dehydration, hyponatremia, hyperkalaemia, and acidosis.

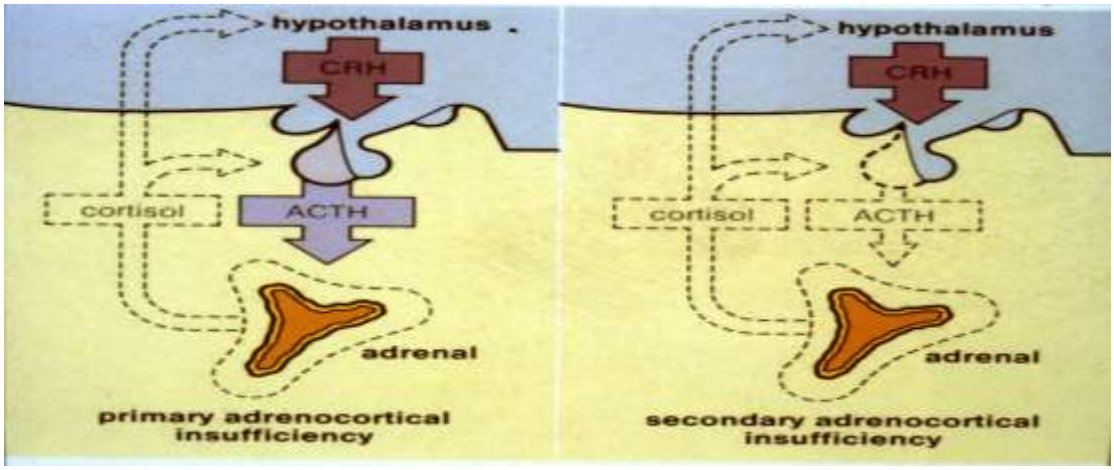
Severe hypoglycaemia is uncommon in adults but can be provoked by fasting, fever, infection or nausea and vomiting .

Amenorrhoea 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.

Laboratory Findings

- Hyponatremia and hyperkalaemia are classical in primary adrenal insufficiency
- There might be normocytic anaemia, neutropenia, eosinophilia and relative lymphocytosis
- Azotaemia 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 adrenocorticol steroids may be normal in partial adrenal insufficiency, test of adrenocortical reserves are necessary to establish the diagnosis.

Rapid ACTH stimulation test: after a baseline cortisol sample is obtained and 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.

The response is normal if the basal plasma cortisol level is greater than 5mcg/dl with an increment greater than 5.7 mcg/dl and a peak level greater than 15-18 mcg/dl at 30 min. Subnormal responses to exogenous ACTH is an indication of decreased adrenal reserve and establish the diagnosis of adrenocortical insufficiency. However, this test does not differentiate between primary and

secondary adrenal insufficiency and ACTH level has to be done. A normal response exclude partial secondary adrenocortical secretion to prevent adrenocortical atrophy but have decreased reserve to stress on hypoglycemia. It this is suspected, pituitary reserves can be tested by insulin induced hypoglycemia or metyrapone test.

Plasma ACTH Levels

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

Metyraphone Testing

Metyraphone blocks cortisol synthesis by inhibiting 11B hydroxylase enzymes that converts 11 deoxy cortisol to cortisol. This stimulates ACTH which in turn increases levels of 11 deoxycortisol. Urinary 17 hydroxycorticosteroid levels also increases. It is used as an overnight test. A normal response indicates normal ACTH secretion and adrenal function.

Secondary Adrenocorticol Insufficiency

The commonest cause of ACTH deficiency is exogenous glucocorticoid administration. Pituitary/hypothalamic tumors are the most common causes of naturally occuring 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.

Basal ACTH and cortisol may be normal but ACTH reserve is impaired and the response to stress is subnormal.

With chronicity there is atrophy of zona fasciculate and reticularis and therefore basal cortisol secretion is decreased. At this stage, the pituitary adren axis is impaired and will not respond to stress and to exogenous ACTH.

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

The hyper-pigmentation is absent because of deficient ACTH and BLPH 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 hyperkalaemia. Hypoglycemia is occasionally the presenting feature.

Treatment of Adrenocorticol Insufficiency

Patients with Addison's disease require life long therapy usually with both glucocorticoids and mineralo-corticoids.

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.(now in recent book the does is lower because we are thinking of over dosing)

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

A state of acute adrenocortical insufficiency occuring in patients with Addison's disease who are exposed to the stress of infection trauma surgery or dehydration.

Clinical Features

- Hypotension and shock
- Fever
- Dehydration and voluem depletion,
- Nausea, vomiting, anorexia
- Weakness, apathy, depressed mentation
- Abdominal Pain
- Hypoglycemia
- Fever

Shock and coma may rapidly lead to death in untreated patients

It should be started as soon as possible once diagnosis suspected.

- Parenteral cortisol is commonly used and if has sufficient mineralocorticoid activity so additional treatment is not required. The dose begin as 100 mg every 6 hrs. and the dose is gradually tapered when condition is stable. Maintenance therapy with oral cortisol with or without a mineralcorticoid is then given.

- Intravenous fluids including glucose and saline are required to correct volume depletion, hypotension and hypoglycemia as well as the acidosis and hyperkalaemia 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

(it is life threating condition so we have to be aware about the condition and try to prevent it and how to prevent it ? by awareness
Explain to the patient who is on cortisol two things
1-When they go through stressful condition they have to double the dose because that what happened in normal human body when we go through any stressful condition the adrenal increases the cortisol production and because of the defected adrenal in those patient they cant do that they have to do it them selves whenever they go through simple infection like flu or any stressful condition ,surgery , or delivery they have to double or treble the dose . in most countries people who are diagnosed with hypoadrenalism or who are in steroids they to wear bracelet or to carry a card to till the medical person that they are on steroid and if they cant increase the steroid themself somebody have to do it for them .)

The patient should be informed about life-long therapy and the need to increase the dose of steroids during illness (it should be at least doubled for minor illnesses) and if symptoms continue, a physician should be called.

If oral therapy cannot be taken because of vomiting or diarrhea, then medical assistance should be sought for parenteral therapy

Hypercortisolism
Cushing's Syndrome

Hypercortisolism could cause by many condition the commonest is iatrogenic , (excessive exogenous steroid)

Chronic gulcocorticoid excess whatever the cause leads to a constellation of symptoms and physical features known as Cushing's syndrome.

The most common cause is iatrogenic i.e. secondary to chronic steroid ingestion.

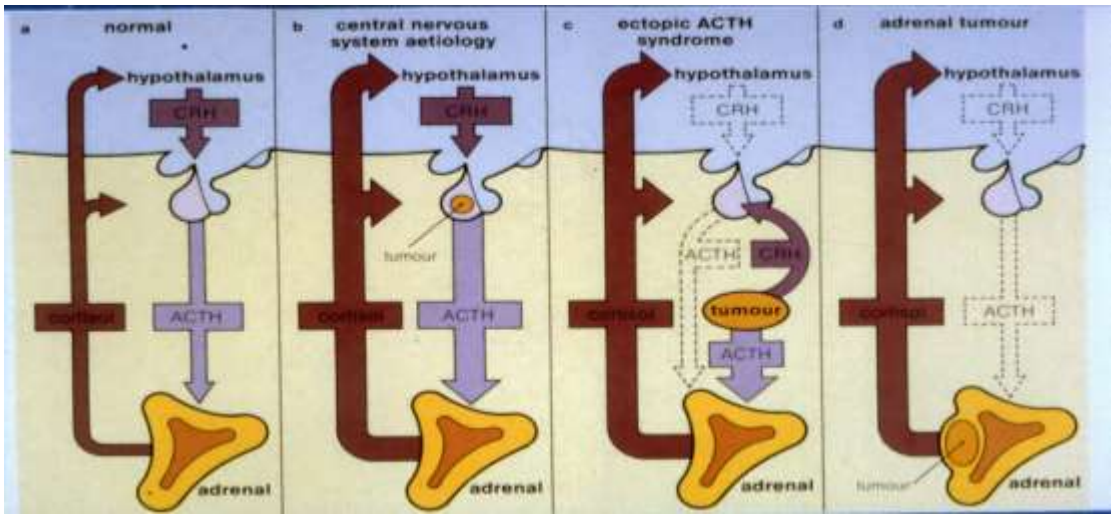
Others causes are:

- ACTH dependent:
  - Cushing's disease 68
  - Ectopic ACTH syndrome 15
- ACTH independent: (rare cause)
  - Adrenal adenoma 9
  - Adrenal carcinom 8

- Cushing's disease is defined as the specific type of cushing's syndrome due to excessive pituitary ACTH secretion (commonly secondary to an adenoma). Women to men ratio is 8:1 and the age of diagnosis is usually between 20-40 yrs.

- In the 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.

Glucocorticoid producing adrenal adenomas and carcinomas arise spontaneously and they are autonomous and not under pituitary hypothalamic control.



Clinical Features

1. **Obesity** (cortisol is anabolic hormone)

The most common manifestation and is classically central affecting mainly the face (moonface) neck, trunk and abdomen with relative sparing of the extremities.

2. **Skin Changes** (because of hypercortisolism as well as the abnormal gonadotropins are suppressed most of the time)

There is thinning of the skin because of atrophy of the epidermis and underlying connective tissue and facial plethora.

They also have striae which are classically red to purple and 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 the ectopic ACTH.

3. **Hirsuitism**

Facial hirsuitism is most common but it can occur anywhere in the body. It is due to the hypersecretion of adrenal androgens. Acne and seborrhea usually accompany the hirsuitism. Virilism is rare and occur in adrenal carcinoma.

4. **Hypertension**

It is a classical feature in Cushing's syndrome and its complications contribute greatly to the morbidity and mortality in the disease.

5. **Gonadal Dysfunction**

This is very common as a result of elevated androgens and cortisol, e.g. amenorrhoea, infertility, decreased libido.

6. **Psychological Distrubances (high cortisol is abnormal to CNS)**

Symptoms range from mild irritability to anxiety, depression, poor memory and concentration to euphoria and mania as well as sleep disorders.
Sever depression and psychosis as well as hallucinations and paranoia can occur.

7. **Muscle Weakness**

Commonly proximal and more prominent in the lower limbs.

8. **Osteoporosis (high cortisol are not good for the bone because they suppress the osteoblast and activate osteoclast)**

A common complication presenting with backpain, and pathological fractures can occur in severe cases.

9. **Renal Calculi**

Occur secondary to hypercalcuria and renal colic may occasionally be a presenting complaint.

10. **Thirst and Polyuria**

Occur secondary to development of diabetes mellitus but asymptomatic glucose intolerance is much more common.



Laboratory & Radiological Findings

High normal haemoglobin and haematocrit are usual with lymphocytopenia and depressed eosinophils count.
Hypokalaemic alkalosis may occur in the setting of ectopic ACTH production.
Most patients have secondary hyper- insulinism and abnormal glucose tolerance tests while some have fasting hyperglycaemia or clinical diabetes mellitus

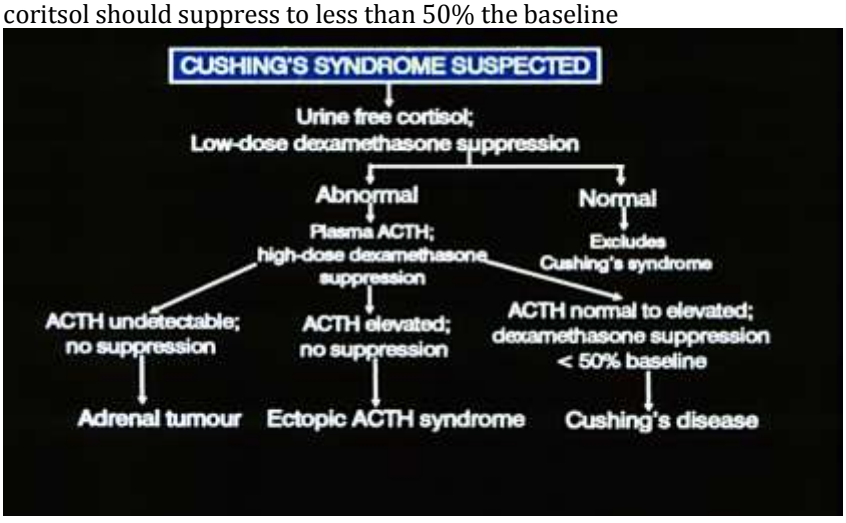
There is hypersecretion of cortisol which is random and episodic with loss of normal circadian rhythm (that is the first clue), therefore plasma cortisol (and ACTH in the ACTH dependent types) remain elevated throughout the day.

- 24- hour urinary free cortisol is an excellent method for diagnosis of Cushing's syndrome and in differentiating it from other forms of hypercortisolism, e.g. obesity
- In Cushing's disease, ACTH is normal or modestly elevated while in the ectopic syndrome, it is markedly elevated. In adrenal tumours, ACTH is undetectable.
- Dexamethasone Suppression Tests
  Establish the presence of a Cushing's syndrome regardless of the cause. It assesses feedback inhibition of the hypothalamic pituitary adrenal axis which is abnormal in Cushing's syndrome.

A. OVERNIGHT 1 MG DEXAMETHASONE SUPPRESSION TEST
   A screening test – the morning cortisol level should fall to below 5 ug/dL. If the test is positive in the absence of conditions causing false positive results. e.g. alcoholism, depression, drugs then the diagnosis should be confirmed by other tests.
B. TWO-DAY LOW DOSE TEST
   Dexamethasone 0.5 mg is given every 6 hours for two days. Plasma cortisol level should suppress to below 5 ug/dL hours after the last dose and the urinary cortisol done in the second day should suppress to below 25 ug/day.

High Dose Tests:

A. OVERNIGH HIGH DOSE DEXAMETHASONE SUPPRESSION TEST
   A simple fast test – The AM cortisol after 8 mg of Dexamethasone given the night before should reduce to less than 50% of the baseline value.
B. TWO-DAY HIGH DOSE TEST
   Dexamethasone 2 mg every 6 hours is given for two days Serum and urine coritsol should suppress to less than 50% the baseline



Radiological

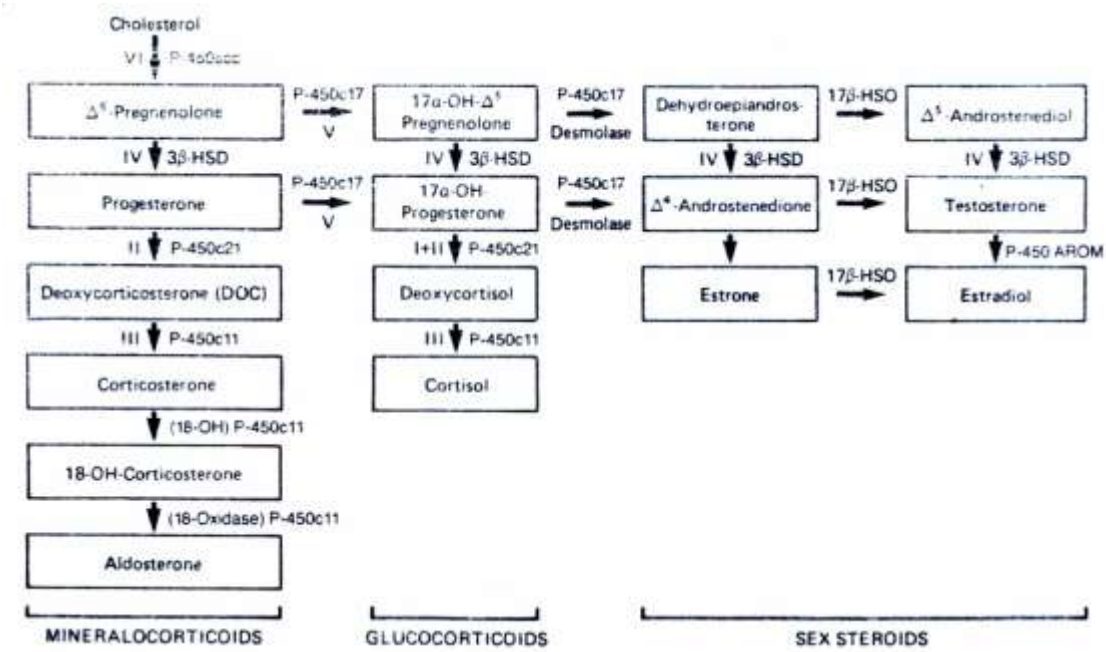
CT scanning will help in localizing pituitary and adrenal tumours and in some instances, ectopic ACTH production. Small tumours may be difficult to detect and selective venous sampling may be needed. In some cases, more detailed isotope scanning and arteriography or venography may be needed

Treatment:

Cushing's Disease – Hypercortisolism has a lot of complications and can be fatal if left untreated.

Treatment is directed at control of ACTH hypersecretion by the pituitary and available methods include:

1. Microsurgery (first line of treatment)
2. Radiotherapy
3. Pharmacological inhibition of ACTH secretion



Drugs:

1.Mitotane acts by inhibiting cortisol synthesis through inhibiting the P450 enzyme responsible for 11B hydroxylation.

2.Metyrapone also blocks cortisol synthesis by inhibiting 11B hydroxylase action and also the cholesterol side-chain cleavage.

3.Ketocenazole is a potent inhibition of the P450 enzymes with a principle effect on the 17-20 lyase enzymes but it also inhibits 11B hydroxylase, 18 hydroxylase and cholesterol side-chain cleavage.

4.Aminoglutethimide acts to inhibit the conversion of cholesterol to pregnenolone.

5.RU486 (Mifepristone) is a potent glucocorticoid receptor antagonist.

They all have major side effects which limit their usefulness as medical therapy except in individual cases.

Ectopic ACTH Syndrome

Therapy is directed at removal of the tumour which is only successful in the benign tumours 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

Primary Mineralocorticoid Excess

The principle mineralocorticoid hormone is aldosterone. It is produced in the zona glomerulosa exclusively and is primarily controlled by the renin-angiotensin system.

Other regulators include:

1.Potassium level

2.ACTH

3.Neural Components of the adrenergic and dopamenergic systems**.**

There is increased production of aldosterone by abnormal zona glomerulosa tissue (adenoma or hyperplasia) which leads to :

- Increased sodium retention
- Expansion of the extracellular fluid volume
- Increased total body sodium content that leads to suppression of renin production.
- Potassium depletion (hypokalemia) occur decreasing the total body and plasma concentration of potassium and producing alkalosis.
- Pseudohypocalcemia because of alkalosis the calcium bind to the protein so the free calcium is low
- Hypertension sometimes
- With moderate potassium depletion. There is decreased carbohydrate tolerance and resistance to antidiuretic hormone.

Because aldosterone biosynthesis is intensified, the entire biosynthetic pathway becomes activated and precursors like DOC corticosterone and 18-hydroxycorticosterone are present in increased amount in person with an aldosterone producing tumour. There is no abnormalities in cortisol production, plasma cortisol levels or cortisol metabolism.

CAUSES

1. Aldosterone producing adenoma (APA) the commonest cause
2. Bilateral adrenal hyperplasia; idiopathic AH
3. Indeterminate hyperaldosteronism
4. Dexamethasone suppressible hyperaldoesteronism
5. Adrenocortical carcinoma

Clinical Features

Patient usually come to medical attention because of symptoms of hypokalaemia or detection of previously unsuspected hypertension.

There are no characteristic symptoms and often nonspecific complaints, e.g. tiredness, lethargy, weakness, nocturia and symptoms of potassium depletion

If potassium depletion is severe with alkalosis, there is increased thirst and polyuria and maybe parasthesia. Headache is a frequent complaint. Blood pressure can range from borderline to severe hypertensive levels.

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- Accelerated/malignant hypertension is rare and a postural fall in blood pressure without reflex tachycardia is observed in severe potassium depletion because of blunting of the baroreceptors.
- Retinopathy is mild with haemorrhages being rare.
- A positive trousseau or chvostek sign may suggest alkalosis with severe potassium depletion. The ECG shows signs of modest LVH and potassium depletion

Laboratory & Radiological Diagnosis

Diuretics should be stopped three weeks prior to potassium measurement. Other features include:

☐A high serum sodium in the presence of reduced haematocrit value (due to increased extracellular fluid and plasma volume from sodium retention)

☐There is also failure to concentrate urine.

☐Abnormal glucose tolerance

☐Alkalosis

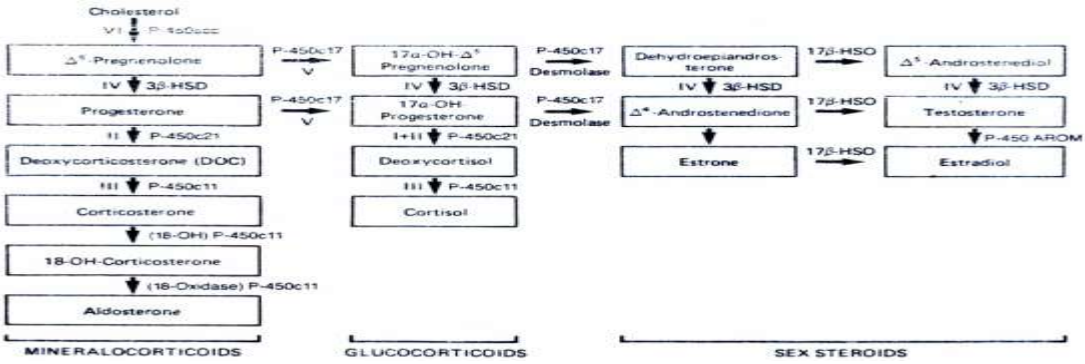
☐All features of potassium depletion

If hypokalaemia is documented, the next step is to assess the renin angiotensin system by doing a random plasma renin activity level and if normal or high in the absence of diuretics therapy, then primary aldosteronism is very unlikely but if it is suppressed, then primary aldosteronism is a likely diagnosis

Measurement of Aldosterone & Other Steroids

Aldosterone – both plasma and urinary aldosterone measurement 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.

It is important to distinguish between adenoma and hyperplasia because surgery is indicated in the former but not in the latter. After at least 4 days of high salt intake and after an overnight recumbency, the 8:00 am aldosterone level is usually greater than 20 mg/dl in adenoma and less than 20 mg/dl in hyperplasia. After 2-4 hours of upright posture (which normally activates the renin system with a rise in aldosterone) the plasma aldosterone level shows no significant change in most patients with adenoma but is almost always increased in hyperplasia



Other Steroids (the doctor didn't mention any thing about the two slides)

Plasma DOC and corticosterone are frequently increased in 8:00 AM in patients with adenoma whereas they are rarely elevated in hyperplasia. 18-Hydroxycorticosterone is invariably increased in patients with adenoma to greater than 85 mg/dl and shows no overlap with the normal or slightly high values in patients with hyperplasia.
In patients, where the above tests are equivocal, further tests can help to establish the diagnosis and also help in further defining the hyperplasia

SALINE INFUSION TEST
Saline loading establishes aldosterone unresponsiveness to volume expansion and thereby identifies autonomy in patients with adenoma or hyperplasia while aldosterone suppresses in indeterminate hyperplasia.
II THE DEOXYCORTICOSTERONE ACETATE MANOUVER (DOC)
Aldosterone is suppressed minimally or not at all by DOC or fludrocortisone in patients with adenoma or hyperplasia but indeterminate hyperaldosteronism can suppress with this manouver.
III GLUCOCORTICOID TREATMENT
The glucocortoid remediable hyperaldoesteronism responds well to administration of ACTH suppressive doses of glucocorticoids (1-2 mg of dexamethasone daily).

Localization of Adenoma/Carcinoma

Scanning using i.v. Administered 1^3 iodocholesterol locates tumour in 80% of the cases depending on the size of the tumour. NP59 scan is another scan which consumes less time.

CT scanning is also useful with less radiation hazard. Other methods include adrenal venography, adrenal vein catheterization and bilateral sampling of blood for aldosterone measurements.

Treatment

In aldosterone producing adenoma, unilateral adrenalectomy is recommended provided there is adequate potassium replacement and adequate extracellular volume expansion with adequate control of BP before surgery all of which can be achieved by spironolactone with or without other medications which should be given for some time before surgery.

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

The surgical cure of hypertension associated with adenoma is excellent as is reported to be over 50% in many series with reduction of hypertension in the remainder

Pheochromocytoma

Very rare

Pheochromocytoma may occur as a heritable disorder either alone or in combination with other endocrine tumours, e.g. MEN type II A – hyperparathyroidism, pituitary adenoma and medullary thyroid carcinoma or MEN Type II B – pheochromocytoma with mucosal neuroma.

The Role of 10

10% bilateral usually unilateral
10% Familial
10% Malignant
10% Extra adrenal

Common extra adrenal sites and near the kidneys and the organ of Zuckerkandl. They can also occur in the posterior mediastinal region.

Clinical Manifestation

Most patients have symptoms that vary in intensity and are perceived to be mainly episodic or paroxysmal by about half the patients.

Most patients with persistent hypertension also have superimposed paroxysms and only few patients are entirely free of symptoms and hypertension between attacks and give no evidence of catecholamine excess during these intervals.

COMMONLY REPORTED SYMPTOMS AND SIGNS

Symptoms during or following paroxysms:

- ☐ Headache
- ☐ Sweating
- ☐ Forceful heart beat with or without tachycardia
- ☐ Anxiety or fear of impending death
- ☐ Tremor
- ☐ Fatigue or exhaustion
- ☐ Nausea and vomiting
- ☐ Abdominal or chest pain
- ☐ Visual disturbances

Symptoms between Paroxysms

Increased sweating, cold hands and feet, weight loss, constipation
In the attack, the symptoms resemble those produced by injection of epinephrine or norepinephrin. An episode usually starts with a sensation of something deep inside the chest and a stimulus to deepen breathing is noted. The patient then becomes aware of a pounding or forceful heartbeat caused by the baroreceptor-mediated increase in cardiac output. This throbbing spreads to the rest of the trunk and head causing a headache or a pounding sensation in the head.

The intense alpha recepto-mediated peripheral vasoconstriction causes cool, moist hands and feet and facial pallor. This combination of increased cardiac output and vasoconstriction causes marked elevation of the blood pressure. The decreased heat loss and increased metabolism cause a rise in temperature and flushing and leads to reflex sweating which may be profuse and usually follows the cardiovascular effects.

The increased glycolysis and alpha receptor-mediated inhibition of insulin release cause an increase in blood sugar levels.

Patient experience anxiety and when episodes are prolonged there may be nausea, vomiting, chest or abdominal pain, visual disturbances, parasthesia or seizures. A feeling of fatigue or exhaustion usually follows the attack. Most of these symptoms can be elicited in all patients but the variability of presenting complaints maybe confusing and is sometimes misleading.

The attacks in pheochromocytoma in those patients with paroxysmal symptoms occur several times a week or oftener and last 15 minutes or less but they may occur at intervals of months or as often as 25 times a day and may last minutes to days. With time the attacks usually increase in frequency but do not change much in character. They are usually precipitated by activities that compress the tumour, e.g changes in position, exercise lifting, defecation or eating and by emotional distress or anxiety.

On the other hand, patients with persistently secreting tumours and chronic symptoms usually experience the symptoms complex in response to transient increases in the release of catecholamines. In addition, they have increased metabolic rate with heat intolerance, increased sweating with weight loss. There is also hyperglycaemia and glucose intolerance

Hypertension is usually present and characteristically there is wide fluctuations and an episode of marked hypertension might be followed by hypotension and shock. The blood pressure typically does not respond to commonly used antihypertensive medications. Chronic constriction of the arterial and venous beds leads to reduction in plasma volume and the inability to further constrict the bed upon arising causes the postural hypotension that is characteristically observed. A mass is felt in the neck or abdomen and palpation may produce a typical paroxysm

Patients with persistent symptoms and hypertension may develop hypertensive retinopathy or nephropathy as well as the other sequelae of hypertension. CVA, CCF and MI are all observed. A significant number were found to have myocarditis post partum.

Other causes of increased sympathetic activity must be thought of:

Angina due to coronary vasospasm
- Severe anxiety state
- Hypertension
- Hypertensive crises associated with
  - § Paraplegia
  - § Tabesansalis
  - § Lead poisoning
  - § Acute porphyria
- Menopausal hot flushes
- Thyrotoxicosis,

Diagnosis

The diagnosis of pheochromocytoma should be considered in the following patients.

a. Patients with paroxysmal symptoms
b. Children with hypertension
c. Adults with severe hypertension not responding to therapy.
d. Hypertensive patients with diabetes or hypermetabolism.
e. Hypertensive patients with symptoms resembling the symptom complex described above or can be evoked by exercise position change .. ect. or certain antihypertensive medications.
f. Patients who become severely hypertensive or go into shock during anesthesia, surgery or obstetric delivery,
g. Patients who have disorders sometimes associated with pheochromocytoma, e.g. neurofibromatosis, mucosal adenomes, medulary carcinoma of thyroid or those who have first degree relatives who have pheochromocytomas or other manifestations of MEN.

Ganglioneuromas and neuroblastomas can produce catecholamines with dopamine being the major product leading to a similar picture resembling pheochromocytoma

Laboratory Diagnostic Tests & Radiological Investigations

In patients with continous hypertension or symptoms, levels of plasma or urinary catecholamines and their metabolites are usually clearly increased, the difficulty arises in patients having brief and infrequent paroxysms with symptom-free intervals and in such cases, sampling of blood or urine should be done during a carefully observed episode to confirm the diagnosis.

TESTS USED

COMPOUND

- (Urine), *Epinephrin Norepinephrin Dopamine
- *Metanephrin Normetanephrin

- Vanilly Mandelic Acid (VMA)
- (Blood) Catecholamines

INTERFERING SUBSTANCES

- May be increased with highly fluorescent compounds, e.g. tetracycline, quinidine as well as food and drugs containing catecholamines, e.g. bananas and other drugs, e.g. methyldopa, ethanol
- Increased by catecholamines, MAOI and others
- Increased by catecholamines and food that contain vanillin or L-dopa. Decreased by Clofibrale and MAOI

In patients with infrequent episodes, it may be useful to induce a paroxysm under supervision (it should not be done for those with angina or other severe symptoms). The infusion of glucagons can induce an attack in 90% of patients with pheochromocytoma, Histamin can also be used for the same purpose.

Once the diagnosis has been established, the tumour must be located prior to surgical removal. CT scanning gives better results than sonography or other radiological tests. MRI is evolving as very specific and excellent technique for detecting pheochromocytomas

Treatment

Treatment is directed toward:

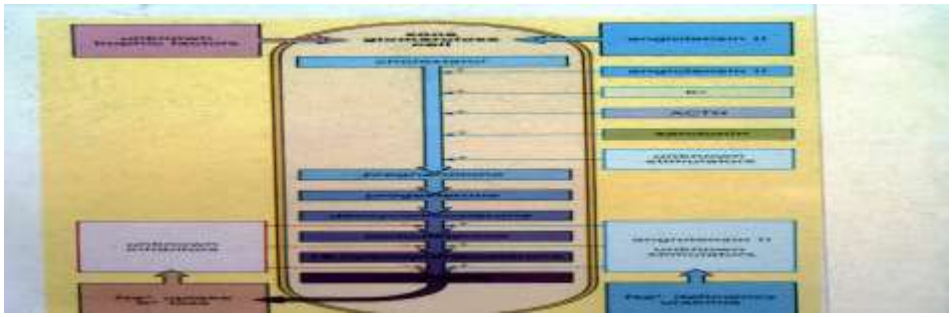
☐ Reduction of symptoms
☐ Lowering of BP
☐ Amelioration of paroxysms

Therapy with alpha adrenergic antagonists should be instituted. Such treatment will allow expansion of the vascular bed and plasma volume. Agents commonly used include phentolamine and phenoxybenzamine, small doses of propranolol maybe required for marked tachycardia or arrythmia prior or during surgery.

Therapy with phenoxybenzamine can be used as a diagnostic test in the occasional patient in whom the chemical tests are inconclusive. A good response in the nature and frequency of attacks as well as on BP indicates the need for re-evaluation of the patient with a strong suspicion for pheochromocytoma

Surgery

Patients should be fully, prepared medically prior to surgery to avoid intra and post operative complications. Once the tumour is removed, the blood pressure usually falls and i.v. fluids and / or blood might be needed to restore circulatory volume. Persistence of high BP after surgery should alert physician to look for other causes, e.g. renal vascular hypertension



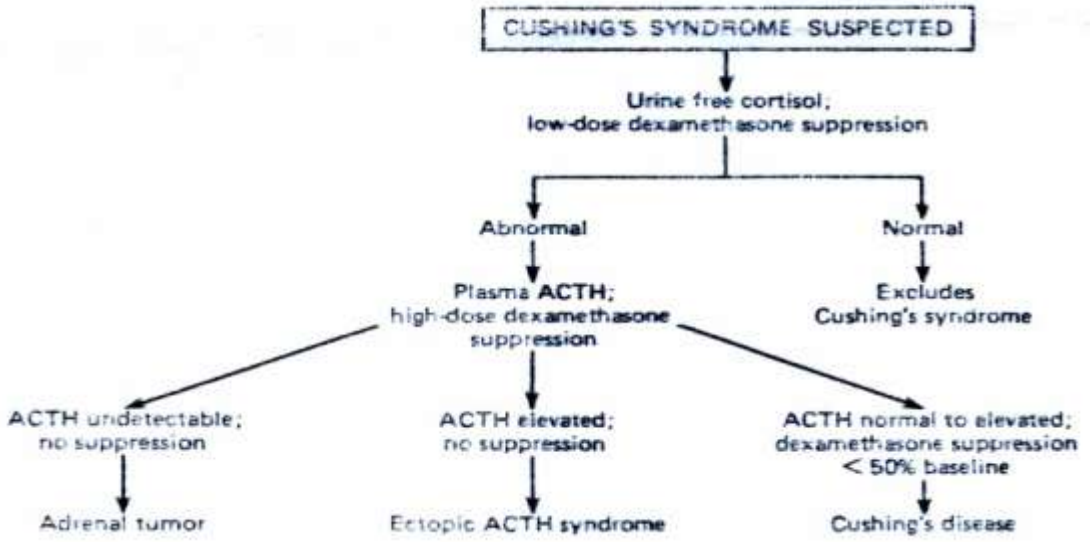
Dexamethasone suppression Tests

1. Low Dose test:

Dexamethasone 0.5 mg is given every 6 hrs. for two days, and 17-hydroxysteroids excretion and free cortisol are measured on the second day of the test. The level should be suppressed to below 4mg/day and >50% respectively. Also serum cortisol level will suppress to <5 mcg/dcl.

1. Screening test:

- Dexamethasone 1 mg overnight test will suppress morning cortisol to less then 3 mcg/dcl in normal patients. This will need other confirmatory tests e.g. UFC.
- False positive results have been seen in depression, with certain medications (Phenytoin and barbiturates) and in patients undergoing stressful events or serious illnesses.



Summary

Primary adenocortical insufficiency

Addison's disease → Major cause is autoimmune (80%)

✓ **Pathophysiology**

Gradual adrenocortical destruction → with normal basal steroid secretion in the initial phase → further loss of cortical tissue → basal secretions become deficient → manifestation of chronic adrenocortical insufficiency

✓ **clinical features**

- chief symptoms are hyper-pigmentation weakness and fatigue, weight loss anorexia, and gastrointestinal disturbances

✓ **Laboratory Findings**

- Hyponatremia and hyperkalaemia
- Azotaemia and increased serum creatinine
- Mild to moderate hypercalcemia

✓ **Diagnostic Tests**

- **Rapid ACTH stimulation test :** after a baseline cortisol sample is obtained and synthetic ACTH called tetracosactrin is and additional cortisol samples are obtained at 30 and 60 min following the injection.
  - response is normal if the basal plasma cortisol is greater than 5mcg/dl
  - Subnormal responses → adrenocortical insufficiency.
- **Plasma ACTH Levels**
  - high in the primary form and low normal or low in secondary forms.

✓ **Secondary Adrenocorticol Insufficiency**

- The commonest cause of ACTH deficiency is exogenous glucocorticoid administration.
- Clinical features → Hyponatremia with no hyperkalaemia. Hypoglycemia is occasionally present

✓ **Treatment of Adrenocorticol Insufficiency**

- Hydrocortisone 25-30 mg/d twice per day
- Fluorocortisone is the mineralocorticoid of choice given in 0.05-0.1 mg/day .

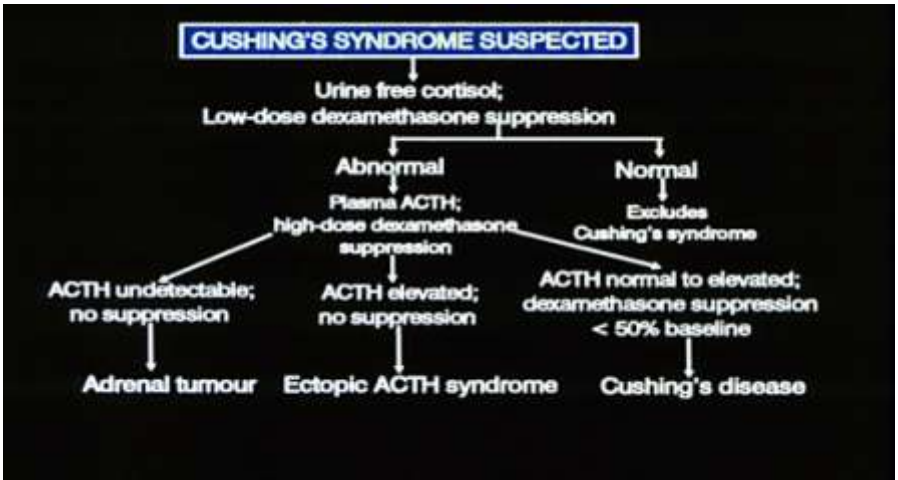
Hypercortisolism (Cushing's Syndrome)

Commonest cause is iatrogenic

✓ **Clinical Features**

- **Obesity , Skin Changes , Hirsuitism , Hypertension , Gonadal Dysfunction Psychological Distrubances , Muscle Weakness , Osteoporosis , Renal Calculi Thirst and Polyuria**

✓ **Laboratory & Radiological Findings**



CT scanning will help in localizing pituitary and adrenal tumors

- ✓ **Treatment:**
  1.Microsurgery (first line of treatment)
  2.Radiotherapy
  3.Pharmacological inhibition of ACTH secretion
  - Drugs are (Mitotane , Metyrapone , Ketocenazole, Aminoglutethimide Mifepristone)
- ✓ **In Ectopic ACTH Syndrome :** removal of the tumor which is only successful in benign tumors
- ✓ **In Adrenal Tumors :** Adenomas are successfully treated by adrenalectomy

Primary Mineralocorticoid Excess

- There is increased production of aldosterone by abnormal zona glomerulosa tissue (adenoma or hyperplasia) which leads to → Increased sodium retention , Expansion of the extracellular fluid volume , Increased total body sodium content , hypokalemia , Hypertension sometimes

Aldosterone producing adenoma (APA) is the commonest cause.

- ✓ **Clinical Features**
  - Hypokalaemia, there is increased thirst and polyuria and maybe parasthesia. Headache is a frequent
- ✓ **Laboratory & Radiological Diagnosis**
  - high serum sodium
  - failure to concentrate urine
  - Abnormal glucose tolerance
  - Alkalosis
  - All features of potassium depletion
- ✓ **Treatment**
  - In aldosterone producing adenoma, unilateral adrenalectomy is recommended

Pheochromocytoma

- The Role of 10 → 10% bilateral usually unilateral , 10% Familial 10% Malignant 10% Extra adrenal
- ✓ **Clinical Manifestation**
  - Most patients with persistent hypertension Headache,Nausea and vomiting ,Forceful heartbeat , Sweating

- ✓ **Laboratory Diagnostic Tests & Radiological Investigations**
  - levels of plasma or urinary catecholamines and their metabolites are usually clearly increased
- ✓ **TESTS USED**
  - urine*Epinephrin Norepinephrin Dopamine , *Metanephri Normetanephrin
  - Vanilly Mandelic Acid (VMA) ,(Blood) Catecholamines
- ✓ **Treatment**
  - directed toward Reduction of symptoms, Lowering of BP and Amelioration of paroxysms . Therapy with alpha adrenergic antagonists should be instituted

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

3- A 50-year-old female is evaluated for hypertension. Her blood pressure is 130/98. She complains of polyuria and of mild muscle weakness. She is on no diuretics or other blood pressure medication. On physical exam, the PMI is displaced to the sixth intercostal space. There is no sign of congestive heart failure and no edema. Laboratory values are as follows:
Na−: 147 meq/dL K−: 2.3 meq/dL Cl−: 112 meq/dL HCO3: 27 meq/dL
The patient is on no other medication. She does not eat licorice.
Which of the following will aid in diagnosis?
a. 24-h urine for cortisol
b. Urinary metanephrine
c. Plasma renin and aldosterone
d. Renal angiogram

4- A 25-year-old woman is admitted for hypertensive crisis. In the hospital, blood pressure is labile and responds poorly to antihypertensive therapy. The patient complains of palpitations and apprehension. Her past medical history shows that she developed hypotension during an operation for appendicitis.
Hct: 49% (37-48) WBC: 11 × 103 mm (4.3-10.8) Plasma glucose: 160 mg/dL (75-115) Plasma calcium: 11 mg/dL (9-10.5)
Which of the following is the most likely diagnosis?
a. Pheochromocytoma
b. Renal artery stenosis
c. Essential hypertension
d. Insulin-dependent diabetes mellitus

Answers

1- the answer is C .This patient's symptoms of weakness, fatigue, and weight loss in combination with signs of hypotension and extensor hyperpigmentation are all consistent with Addison's disease (adrenal insufficiency). Tuberculosis can involve the adrenal glands and result in adrenal insufficiency. Measurement of serum cortisol baseline and then stimulation with ACTH will confirm the clinical suspicion. The ACTH stimulation test is used to determine the adrenal reserve capacity for steroid production. Cortisol response is measured 60 min after cosyntropin is given intramuscularly or intravenously.

2- the answer is B .Hydrocortisone is the mainstay of treatment. Two-thirds of the dose is taken in the morning and one-third at night in order to approach normal diurnal variation. The recommended dose is 20 to 30 mg/d. The mineralocorticoid component of adrenal hormones also needs to be replaced. Fludrocortisone is given at a dosage of 0.05 to 0.1 mg/d. During periods of intercurrent stress or illness, higher doses of both glucocorticoid and mineralocorticoid are required.

3- the answer is C .The patient has diastolic hypertension with associated hypokalemia. She is not taking diuretics.There is no edema on physical exam. Excessive inappropriate aldosterone production will produce a hypertension with hypokalemia syndrome. Hypersecretion of aldosterone increases distal tubular exchange of sodiumfor potassium with progressive depletion of body potassium. The hypertension is due to increased sodium absorption. Very low plasma renin that fails to increase with appropriate stimulus (such as volume depletion) and hypersecretion of aldosterone suggest the diagnosis of primary hyperaldosteronism. Suppressed renin activity occurs in about 25% of hypertensive patients with essential hypertension. Lack of suppression of aldosterone is also necessary to diagnose primary aldosteronism. High aldosterone levels that are not suppressed by saline loading prove that there is a primary inappropriate secretion of aldosterone. A 24-h urine for free cortisol would be used in the workup of a patient with Cushing syndrome. Urinary metanephrine is a screening test for pheochromocytoma.

4- the answer is A . A hypertensive crisis in this young woman suggests a secondary cause of hypertension. In the setting of palpitations, apprehension, and hyperglycemia, pheochromocytoma should be considered. Pheochromocytomas are derived from the adrenal medulla. They are capable of producing and secreting catecholamines. Unexplained hypertension associated with surgery or trauma may also suggest the disease. Clinical symptoms are the result of catecholamine secretion. For example, the patient's hyperglycemia is a result of a catecholamine effect of insulin suppression and stimulation of hepatic glucose output. Hypercalcemia has been attributed to ectopic secretion of parathormone-related protein. Renal artery stenosis can cause severe hypertension but would not explain the systemic symptoms or laboratory abnormalities in this case.