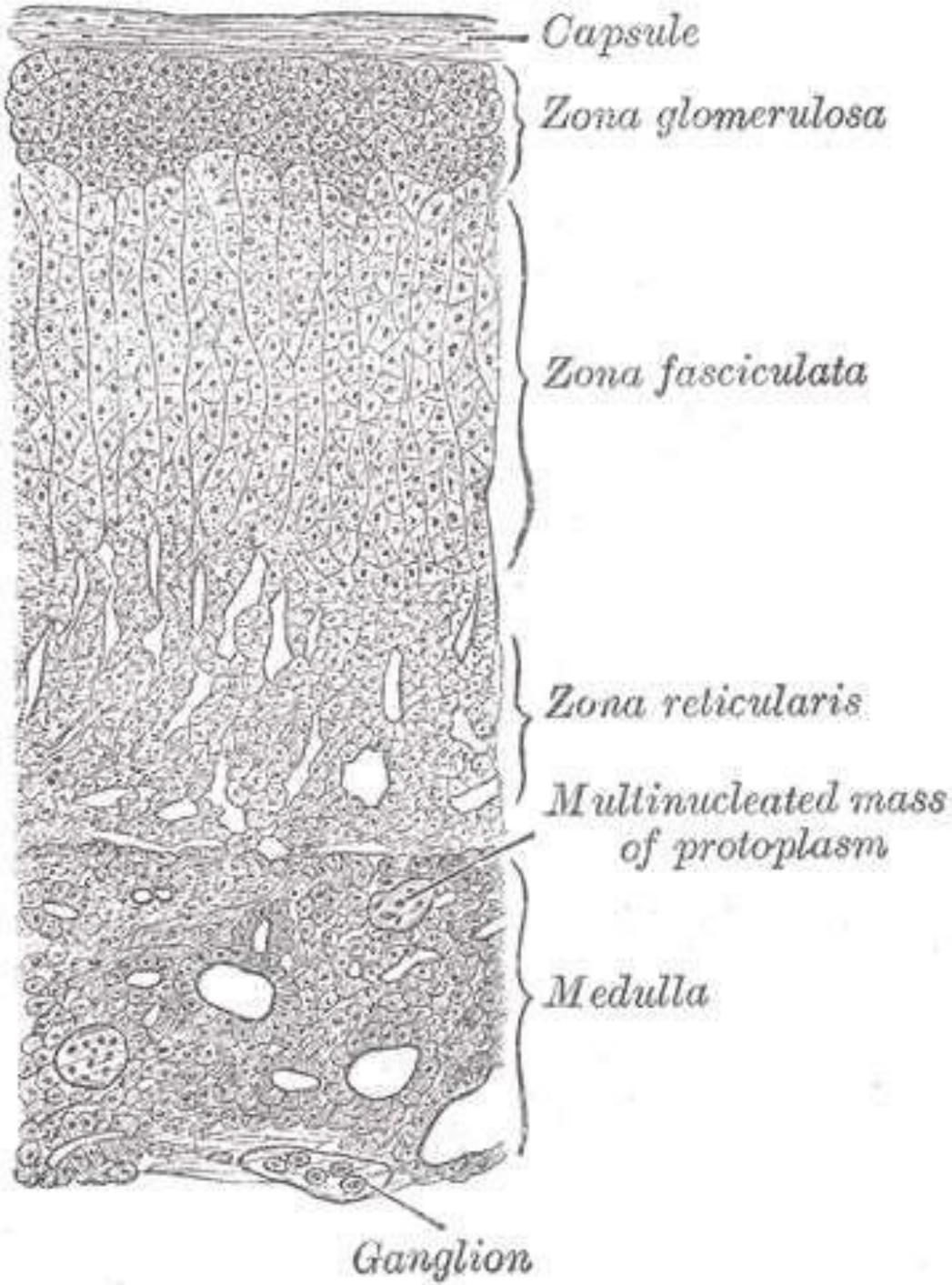
ENDOCRINOLOGY

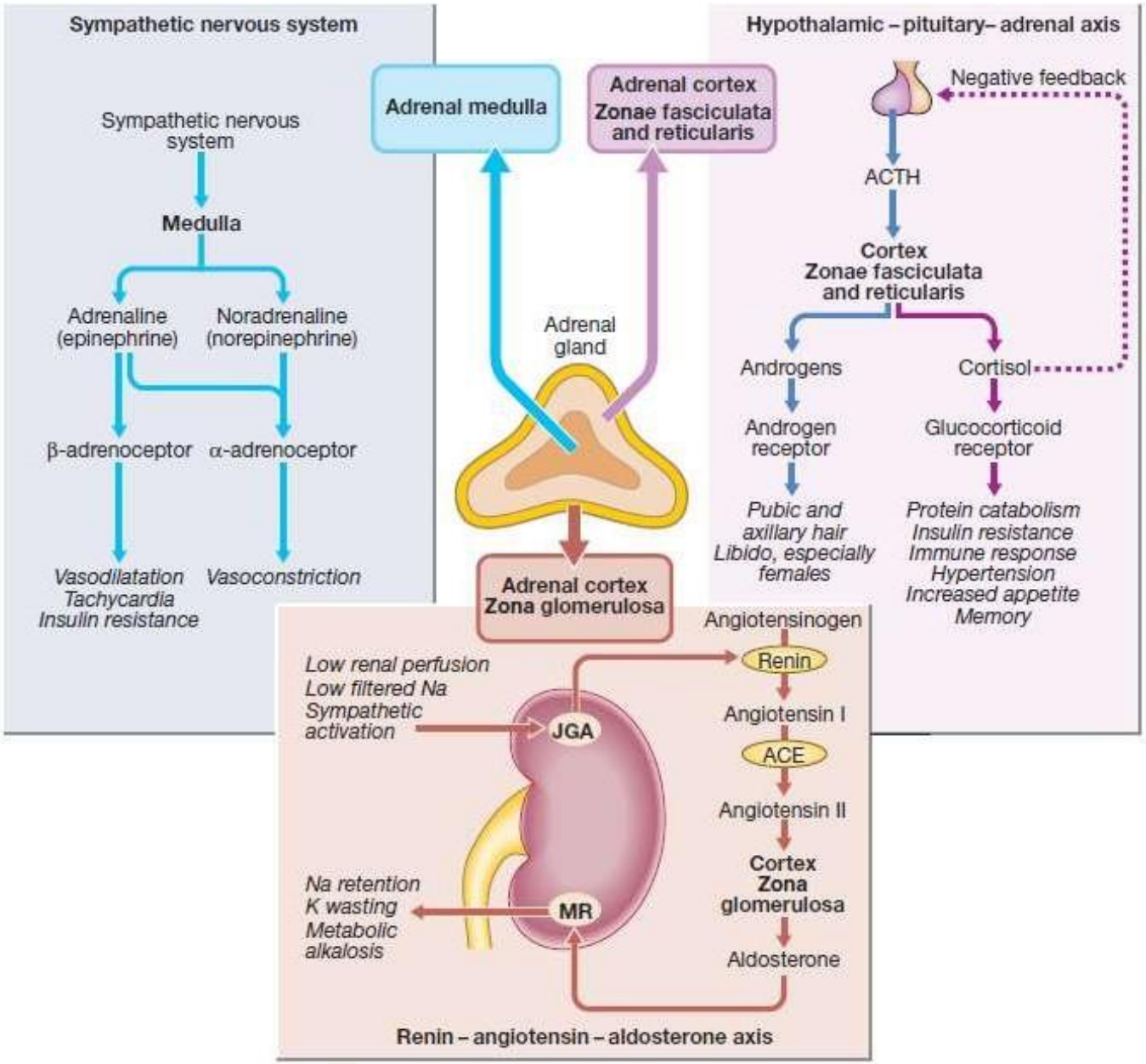
Lecture 1

Adrenal Gland Disorders

Cushing syndrome

Dr. Khalid Shahab


Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Multinucleated mass of protoplasm
Medulla
Ganglion


Sympathetic nervous system
Sympathetic nervous system
Medulla
Adrenaline (epinephrine)
Noradrenaline (norepinephrine)
β-adrenoceptor
α-adrenoceptor
Vasodilatation
Tachycardia
Insulin resistance
Vasoconstriction
Adrenal medulla
Adrenal cortex
Zonae fasciculata and reticularis
Adrenal gland
Adrenal cortex
Zona glomerulosa
Hypothalamic – pituitary– adrenal axis
Negative feedback
ACTH
Cortex
Zonae fasciculata and reticularis
Androgens
Cortisol
Androgen receptor
Glucocorticoid receptor
Pubic and axillary hair
Libido, especially females
Protein catabolism
Insulin resistance
Immune response
Hypertension
Increased appetite
Memory
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Cortex
Zona glomerulosa
Aldosterone
Low renal perfusion
Low filtered Na
Sympathetic activation
JGA
Na retention
K wasting
Metabolic alkalosis
MR
Renin – angiotensin – aldosterone axis

Cushing's Syndrome

Cushing’s syndrome is caused by excessive activation of glucocorticoid receptors. It is most commonly iatrogenic (exogenous), due to prolonged administration of synthetic glucocorticoids such as prednisolone.

18.38 Classification of endogenous Cushing's syndrome

ACTH-dependent – 80%

- Pituitary adenoma secreting ACTH (Cushing's disease) – 70%
- Ectopic ACTH syndrome (bronchial carcinoid, small-cell lung carcinoma, other neuro-endocrine tumour) – 10%

Non-ACTH-dependent – 20%

- Adrenal adenoma – 15%
- Adrenal carcinoma – 5%
- ACTH-independent macronodular hyperplasia; primary pigmented nodular adrenal disease; McCune–Albright syndrome (together <1%)

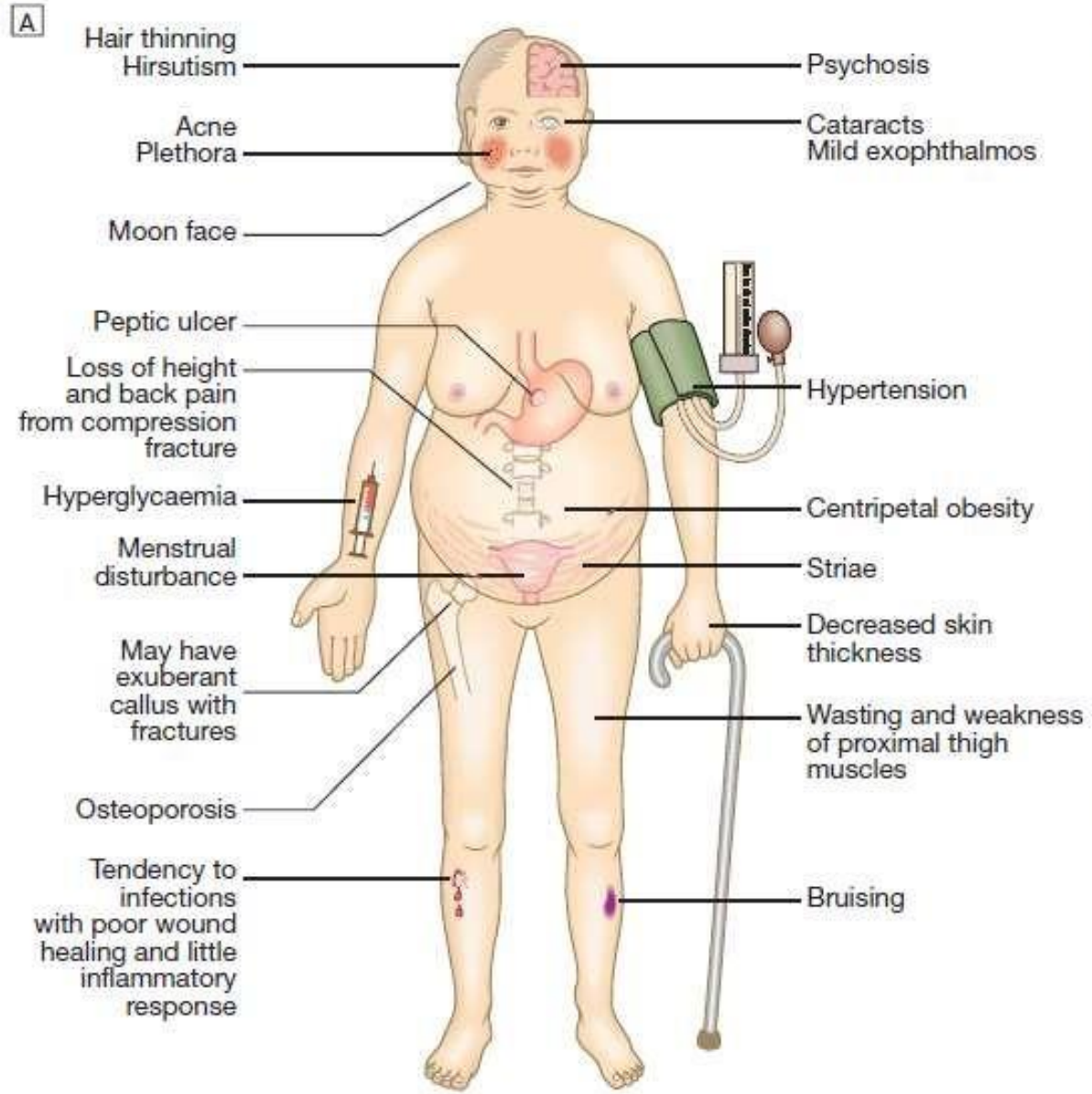
Hypercortisolism due to other causes (also referred to as pseudo-Cushing's syndrome)

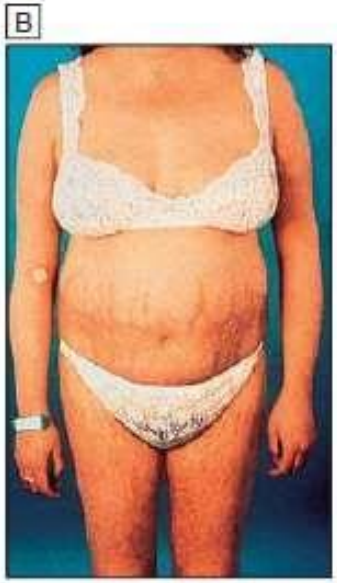
- Alcohol excess (biochemical and clinical features)
- Major depressive illness (biochemical features only, some clinical overlap)
- Primary obesity (mild biochemical features, some clinical overlap)

- Iatrogenic Cushing's syndrome is the most common cause.
- Cushing's disease caused by microadenoma of the pituitary with bilateral adrenal hyperplasia. Both Cushing’s disease and cortisol-secreting adrenal tumours are four times more common in women than men, usually in the young age. In contrast, ectopic ACTH syndrome (often due to a small-cell carcinoma of the bronchus) is more common in men.

Clinical features

1. Truncal obesity with moon face and buffalo hump in the interscapular area..
2. Plethoric face with acne and hirsutism.
3. Easy bruising of skin and violaceous striae in the abdomen and thighs.
4. Proximal myopathy and osteoporosis.
5. Hypertension and hyperglycemia.
6. Oligmenorrhea.
7. Emotional upset and psychosis.


A
Hair thinning
Hirsutism
Acne
Plethora
Moon face
Peptic ulcer
Loss of height and back pain from compression fracture
Hyperglycaemia
Menstrual disturbance
May have exuberant callus with fractures
Osteoporosis
Tendency to infections with poor wound healing and little inflammatory response
Psychosis
Cataracts
Mild exophthalmos
Hypertension
Centripetal obesity
Striae
Decreased skin thickness
Wasting and weakness of proximal thigh muscles
Bruising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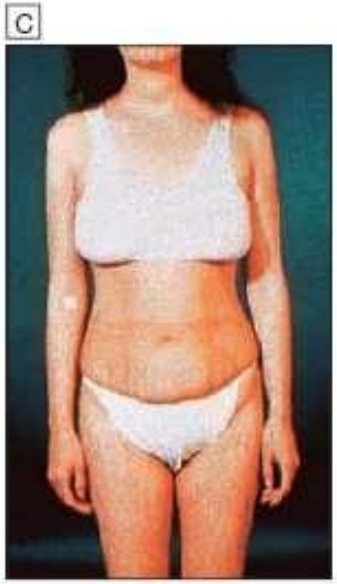
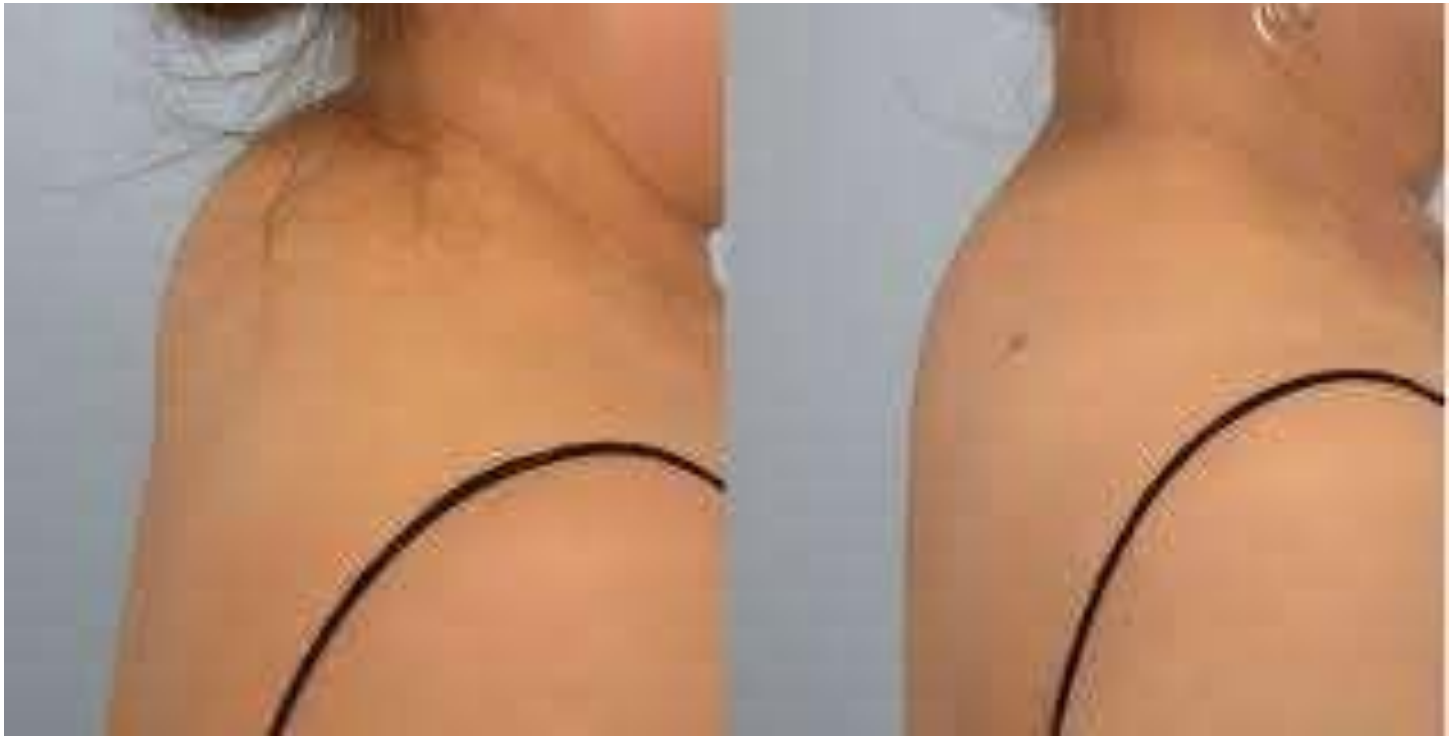
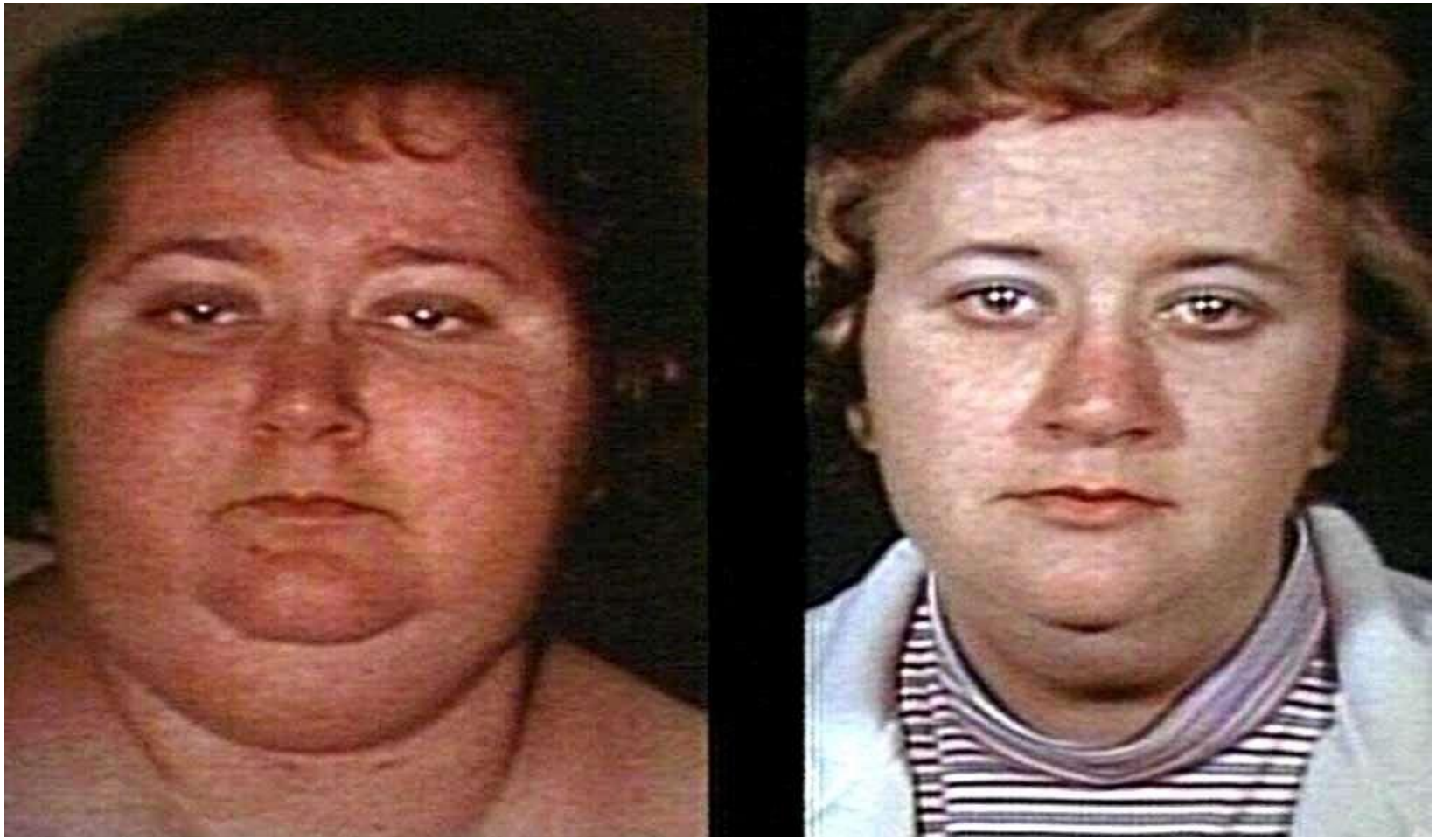

C

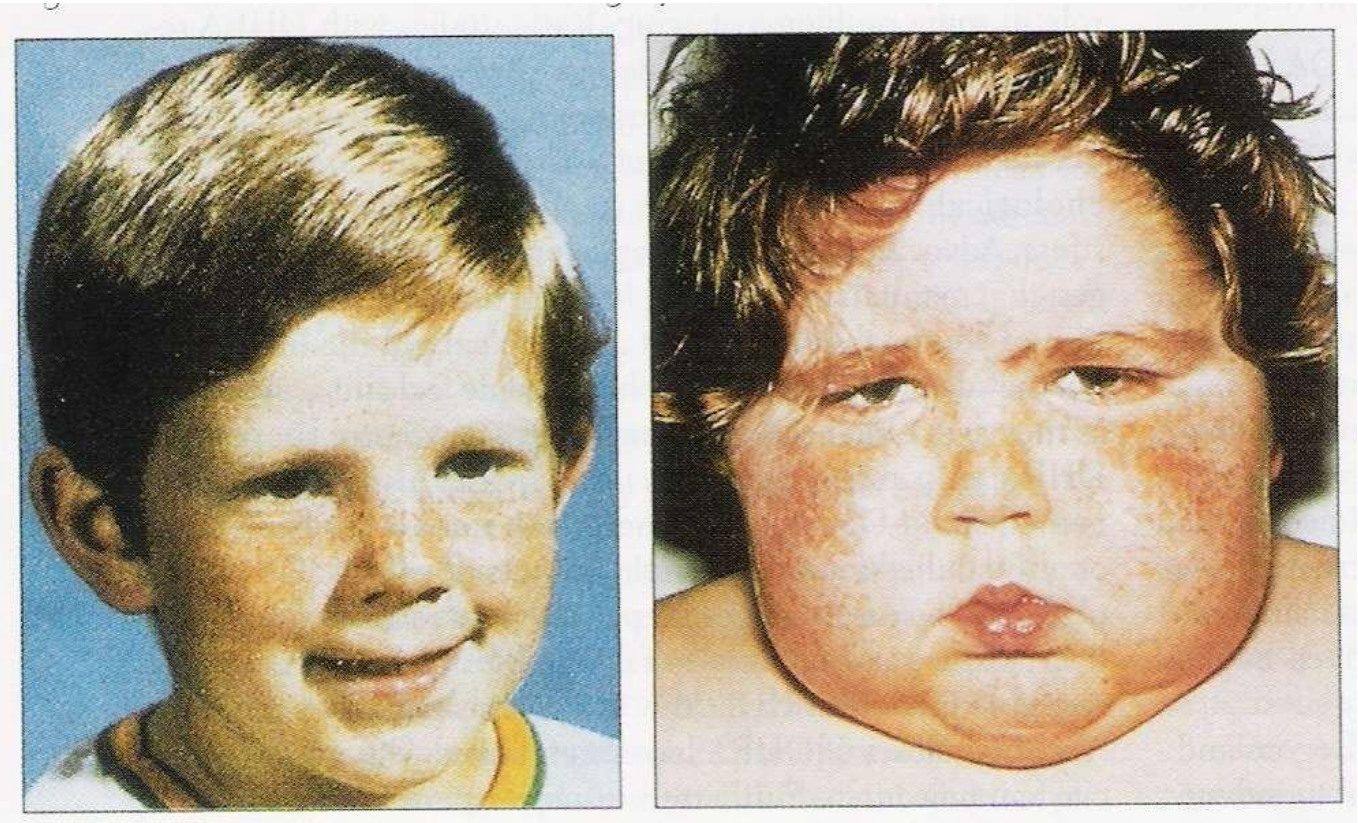
Buffalo hump



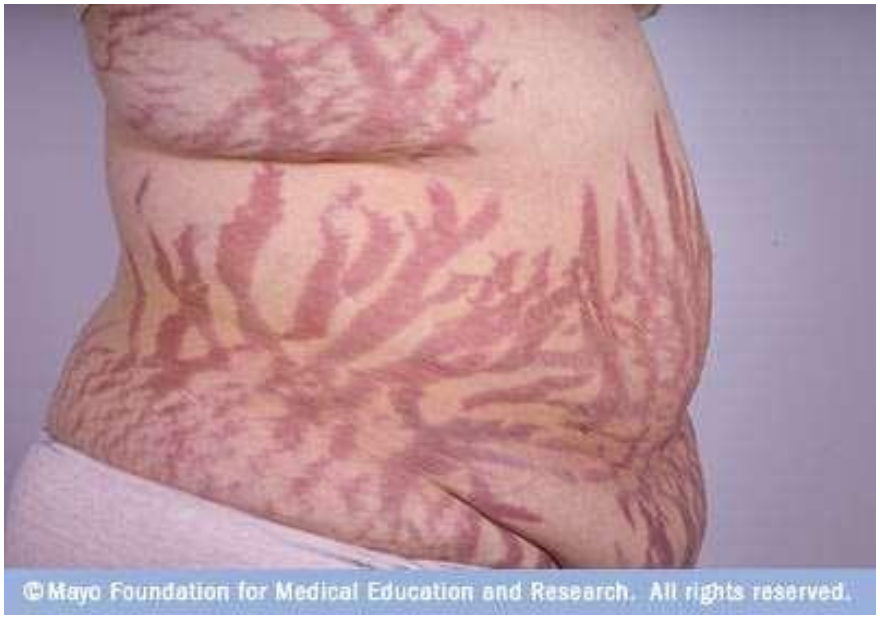
Cushing's Syndrome



Cushingoid face



Striae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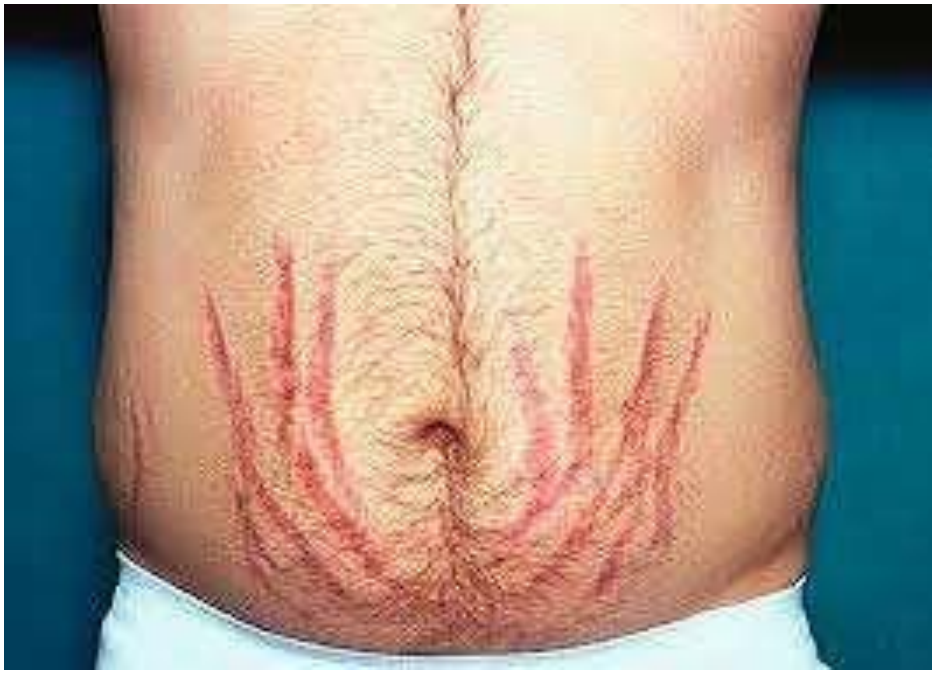


Diagnosis

The diagnosis of Cushing's is a two-step process:

1.to establish whether the patient has Cushing's syndrome.

2. to define its cause.

Some additional tests are useful in all cases of Cushing's syndrome, including plasma electrolytes, glucose, glycosylated haemoglobin and bone mineral density measurement.

Investigations

1. Urine free cortisol(> 2 tests): 24-hr timed collection. Normal range depends on assay
2. Overnight dexamethasone suppression test: the patient given dexamethasone 1mg at 2300 hrs and measuring serum cortisol at 0900 hrs the following day. Plasma cortisol > 50 nmol/L (> 1.81 μg/dL) suggest Cushing'syndrome
3. Low dose dex. suppression test: the patient given dex. 0.5 mg qid for two days. Plasma cortisol > 50 nmol/L (> 1.81 μg/dL) suggest Cushing'syndrome.

Establishing the presence of Cushing's syndrome

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 the normal circadian rhythm of cortisol, with inappropriately elevated late-night serum or salivary cortisol.
3. Increased 24-hour urine free cortisol

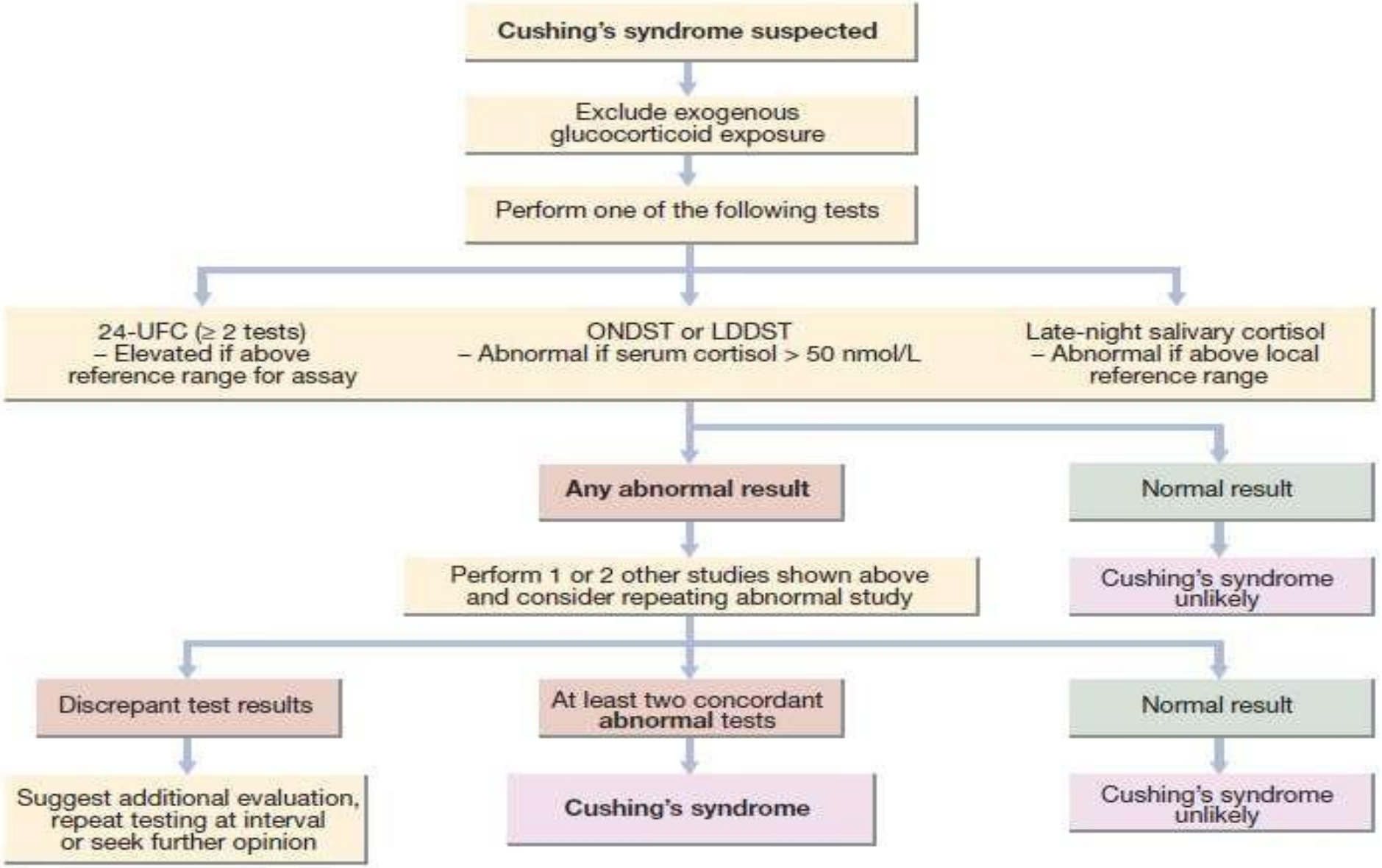


Fig. 18.21 Sequence of investigations in suspected spontaneous Cushing's syndrome. A serum cortisol of 50 nmol/L is equivalent to 1.8 μg/dL. (LDDST = low-dose dexamethasone suppression test; ONDST = overnight dexamethasone suppression test; UFC = urinary free cortisol)

- It is important for any oestrogens to be stopped for 6 weeks prior to investigation to allow corticosteroid-binding globulin (CBG) levels to return to normal and to avoid false-positive responses, as most cortisol assays measure total cortisol, including that bound to CBG.

- Use of multiple salivary cortisol samples over weeks or months can be of use in diagnosis, but an elevated salivary cortisol alone should not be taken as proof of diagnosis.

Determining the underlying cause of confirmed Cushing's syndrome.

4. ACTH level: in the presence of excess cortisol secretion, an undetectable ACTH (< 1.1 pmol/L (5 ng/L)) indicates an adrenal cause, while ACTH levels greater than 3.3 pmol/L (15 ng/L) suggets a pituitary cause or ectopic ACTH.

5. High dose dex. suppression test:

Used for differentiation between pituitary adenoma and other causes. Serum cortisol is measured before and after administration of 2 mg of dexamethasone 4 times daily for 48 hour. If the cortisol is < 50% reduced from baseline suggests ectopic ACTH syndrome; If > 50% reduced from baseline suggests pituitary-dependent disease.

6. Bilateral inferior petrosal sinus sampling (BIPSS): with mesurement of ACTH is the best means of confirming Cushing's disease.

7. MRI or CT of pituitary & adrenal glands.

MRI detects around 60% of pituitary microadenomas secreting ACTH.

CT or MRI detects most adrenal tumours; adrenal carcinomas are usually large (> 5 cm) and have other features of malignancy.

Treatment

- Pituitary microadenoma with adrenal hyperplasia treated by:

1- Trans-sphenoidal surgery carried out by an experienced surgeon with selective removal of the adenoma is the treatment of choice, with approximately 70% of patients going into immediate remission. Around 20% of patients suffer a recurrence, often years later, emphasising the need for life-long follow-up.

2- Laparoscopic bilateral adrenalectomy performed by an expert surgeon effectively cures ACTH-dependent Cushing's syndrome → Nelson syndrome with an invasive pituitary macroadenoma and very high ACTH levels causing pigmentation. The risk of Nelson's syndrome may be reduced by pituitary irradiation.

Adrenal tumours

- Laparoscopic adrenal surgery is the treatment of choice for adrenal adenomas. Surgery offers the only prospect of cure for adrenocortical carcinomas, but in general, prognosis is poor with high rates of recurrence, even in patients with localised disease at presentation. Radiotherapy to the tumour bed reduces the risk of local recurrence, and systemic therapy consists of the adrenolytic drug mitotane and chemotherapy, but responses are often poor.

- Medical blocking of steroidogenesis by ketonazole or metyrapone. Typical starting doses are 250 mg PO q4hr for metyrapone (not to exceed 6g/day) and 600-800 mg/day PO for ketoconazole.
- Somatostatin analogue: pasireotide is indicated for treatment of patients whom pituitary surgery is not an option or has not been curative.

ENDOCRINOLOGY

Lecture 2

Addison's disease & Pheochromocytoma

Adrenal insufficiency

1. Primary (Addison's disease (⇑ ACTH)):
   it is a rare condition, occurs at any age and caused by: autoimmune atrophy, HIV/AIDS, tuberculosis, bilateral hemorrhage, lymphoma and metastatic carcinoma, amylodosis, & haemochromatosis. Adrenal failure may be part of PAS I or PAS II.

- Secondary adrenal failure (⇓ ACTH): Withdrawal of suppressive glucocorticoid therapy & Hypothalamic or pituitary disease, which is the most common cause of adrenal insufficiency.

18.41 Causes of adrenocortical insufficiency

Secondary (↓ACTH)

- Withdrawal of suppressive glucocorticoid therapy
- Hypothalamic or pituitary disease

Primary (↑ACTH)

Addison's disease

Common causes

- Autoimmune:
  - Sporadic
  - Polyglandular syndromes (p. 688)
- Tuberculosis
- HIV/AIDS
- Metastatic carcinoma
- Bilateral adrenalectomy

Rare causes

- Lymphoma
- Intra-adrenal haemorrhage (Waterhouse–Friderichsen syndrome following meningococcal sepsis)
- Amyloidosis
- Haemochromatosis

Corticosteroid biosynthetic enzyme defects

- Congenital adrenal hyperplasias
- Drugs: metyrapone, ketoconazole, etomidate

Clinical features

(Addison's disease)

Gradual adrenal destruction is characterized by an insidious onset of fatigability, malaise, anorexia, nausea and vomiting, weight loss, cutaneous and mucosal pigmentation, hypotension, and hypoglycemia.

Symptoms:

Fatigue, lassitude, malaise, weakness, anorexia

Postural dizziness, syncope

Gastrointestinal Symptoms
- *Nausea*
- *Vomiting*
- *Abdominal Pain*
- *Diarrhea*
- *Constipation*

Myalgias, arthralgias, rarely flexion contractures

Decreased libido, amenorrhea

Signs:

Weight loss

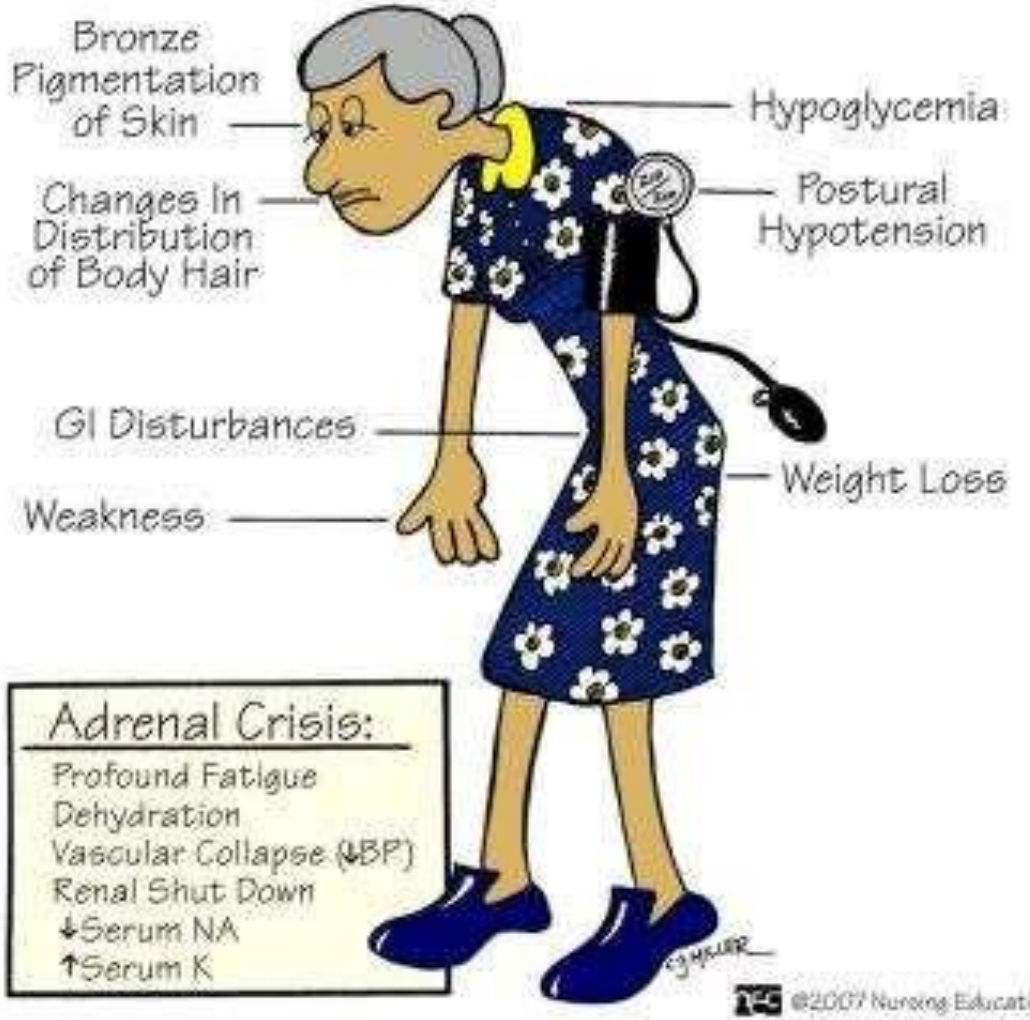
Hyperpigmentation

Hypotension

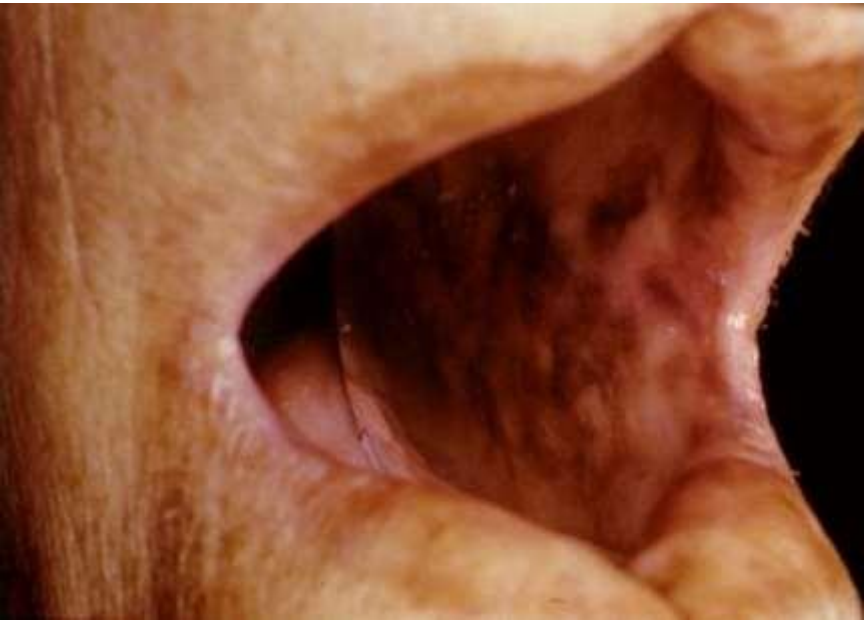
Thinning of axillary and pubic hair

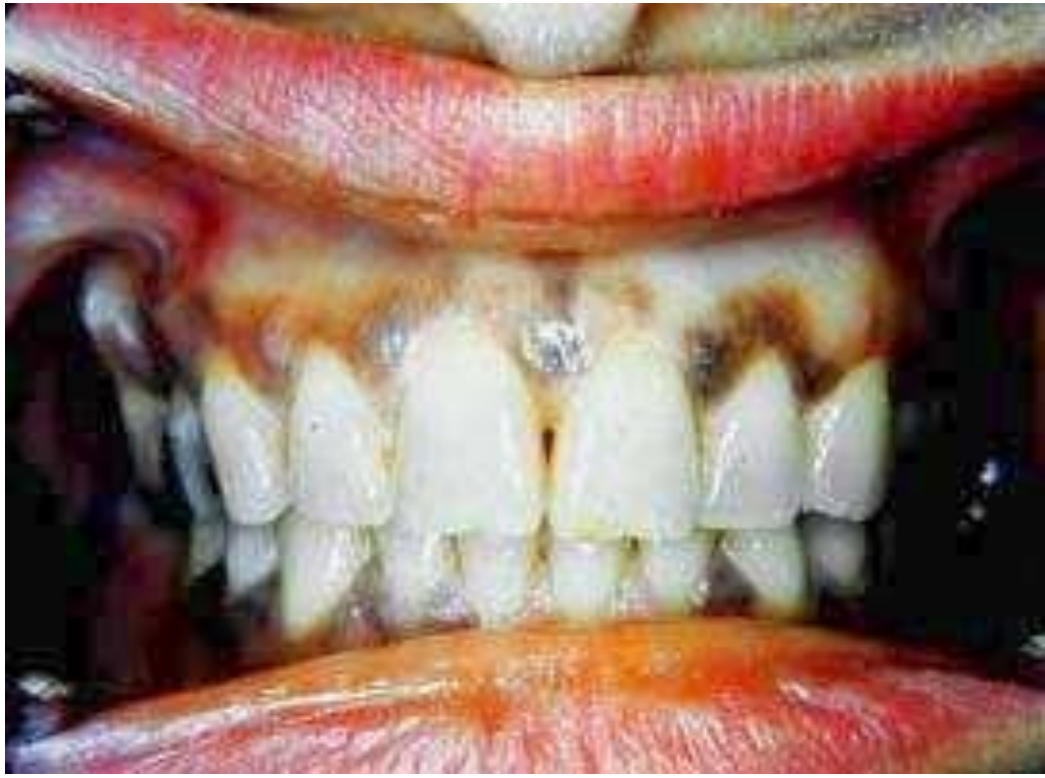
Vitiligo

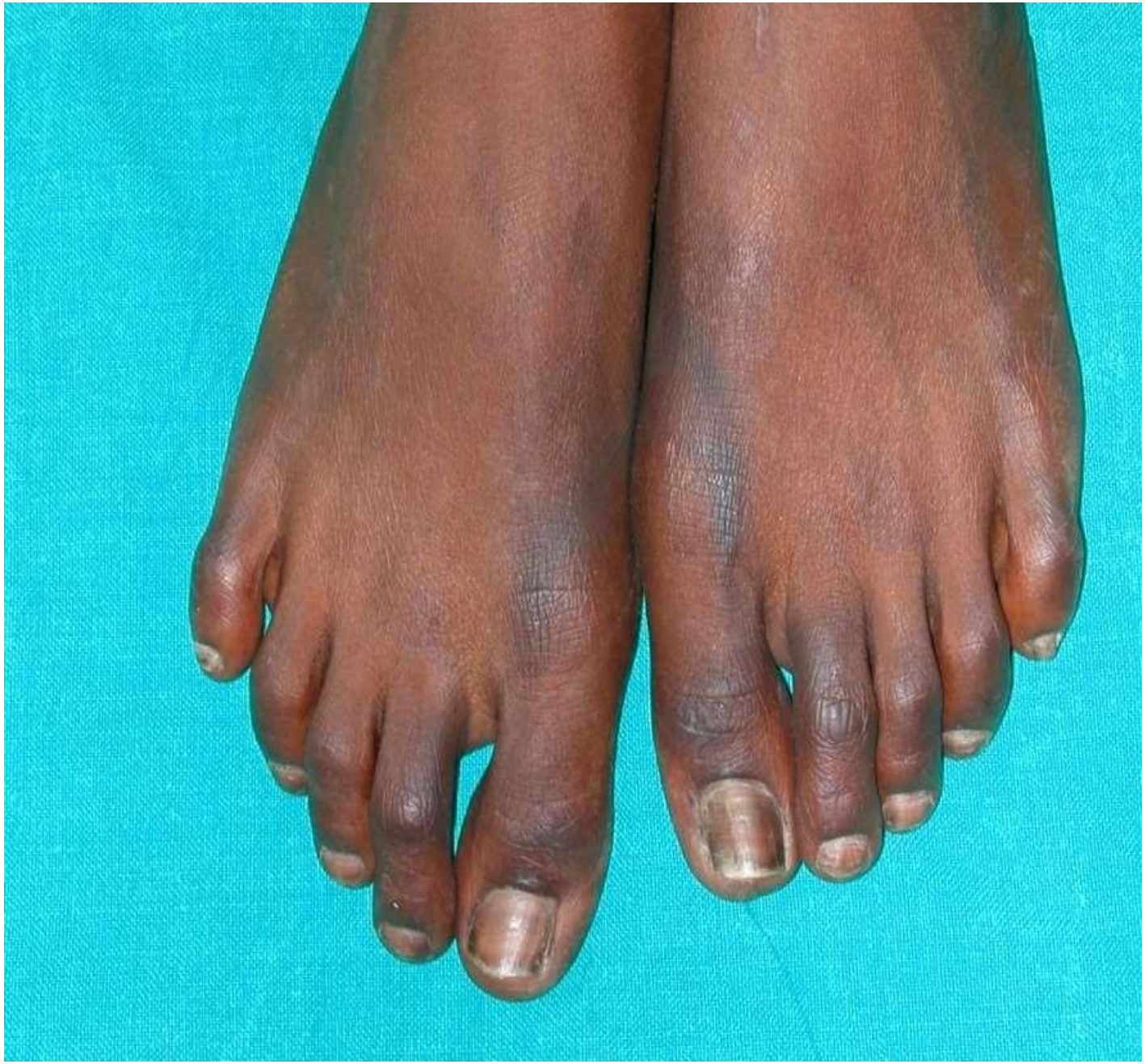
ADDISON'S DISEASE



Hyperpigmentation of mucous membrane in Addison's disease







Adrenal crisis

- Acute adrenal insufficiency caused by adrenal hemorrhage or by sudden withdrawal of prolonged steroid therapy.
- The patient presents with significant hypotension and hypoglycemia and even in shock.

Diagnosis

1. General: hyponatremia, hyperkalemia.
2. ACTH (Synacthen) stimulation test: it is the best screening test in which plasma cortisol measured 30 min after im injection of 250 ug ACTH; normally cortisol levels should exceed 500 nmol/L (18 ug/ dL).
3. ACTH and aldosterone level help in differentiation between primary and secondary adrenal failure.

Treatment

1. Corticosteroid replacement in form of cortisol 15-20 mg/d or prednisolone 5 -7.5 mg/d (2/3 on waking and 1/3 at 1500 hrs). The dose should be doubled in acute stressful conditions like infection and surgery.

2. Mineralcorticoid replacement in form of fludrocortisone 0.05-0.15mg/d with adequate salt intake and monitoring the dose by measuring electrolytes and blood pressure.
3. Acute adrenal failure (addison crisis) is treated by parenteral steroid in form of hydrocortisone and normal saline replacement.

Adrenal crisis

is an acute adrenal insufficiency

This condition requires immediate treatment including:

IV injection of a glucocorticoid—usually a 100-mg hydrocortisone

fluid and electrolyte replacement

Over the first 24 hours, 100 mg is administered IV slowly every 6 to 8 hour

if needed, blood pressure is supported with fluid replacement and vasopressors, along with correction of hypoglycemia

Secondary adrenal insufficiency

- Hyperpigmentation is absent, other endocrine disorders may be present.
- Aldosterone is near normal.
- Iatrogenic type associated with low cortisol and ACTH due to prolonged suppression of the pituitary.

Pituitary insufficiency is treated with cortisol replacement, iatrogenic type treated by gradual tapering of steroid therapy and some times with ACTH to stimulate the pituitary and this may take days to months.

Pheochromocytomas and paraganglioma

- These are rare neuro-endocrine tumours that may secrete catecholamines (adrenaline/epinephrine, noradrenaline/ norepinephrine). Approximately 80% of these tumours occur in the adrenal medulla (phaeochromocytomas), while 20% arise elsewhere in the body in sympathetic ganglia (paragangliomas).

Pathology

- In adults, approximately 80% of pheochromocytomas are unilateral and solitary, 10% are bilateral, 10% are extraadrenal and about 10% are malignant.
- Most are benign but approximately 15% show malignant features. Around 40% are associated with inherited disorders, including neurofibromatosis, von Hippel–Lindau syndrome, MEN 2 and MEN 3.

Clinical features

18.47 Clinical features of phaeochromocytoma

- Hypertension (usually paroxysmal; often postural drop of blood pressure)
- Paroxysms of:
  - Pallor (occasionally flushing)
  - Palpitations, sweating
  - Headache
  - Anxiety (angor animi)
- Abdominal pain, vomiting
- Constipation
- Weight loss
- Glucose intolerance

Clinical features

1. Hypertension: is the most common presentation. Although it has been estimated that phaeochromocytoma accounts for less than 0.1% of cases of hypertension. The presentation may be with a complication of hypertension, such as stroke, myocardial infarction, left ventricular failure, hypertensive retinopathy or accelerated phase hypertension.

2. Panic paroxysms (crisis): occur in 50% of patients.

- The attack characterized by headache, profuse sweating, palpitations, and apprehension associated with pallor or flushing. Abdominal pain & vomiting may occur. The blood pressure is elevated.
- The paroxysms may be frequent or sporadic.
- The paroxysm may be precipitated by any activity that displaces the abdominal contents or occurs spontaneously.
- The attack may last from a few minutes to several hours.

3. Postural drop of blood pressure: may occur as a result of diminished plasma volume (pressure natriuresis).

4. Other features are weight loss, glucose intolerance, constipation, polycythemia and Hypercalcemia.

Clinical Features

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

Diagnosis

- The diagnosis is confirmed by measurement of plasma and/or urinary excretion of metanephrine, or normetanephrine.

- There is a high ‘false-positive’ rate, as misleading metanephrine concentrations may be seen in stressed patients (during acute illness, following vigorous exercise or severe pain) and following ingestion of some drugs such as tricyclic antidepressants. For this reason, a repeat sample should usually be requested if elevated levels are found, although, as a rule, the higher the concentration of metanephrines, the more likely the diagnosis of phaeochromocytoma/paraganglioma.

- Serum chromogranin A is often elevated and may be a useful tumour marker in patients with non-secretory tumours and/ or metastatic disease.
- Localization of the tumor is done by abdominal CT scan or MRI. Localisation of paragangliomas may be more difficult. Scintigraphy using meta-iodobenzyl guanidine (MIBG) can be useful, particularly if combined with CT, for adrenal phaeochromocytoma but is often negative in paraganglioma.

Treatment

- In functioning tumours, medical therapy is required to prepare the patient for surgery, preferably for a minimum of 6 weeks, to allow restoration of normal plasma volume. The most useful drug in the face of very high circulating catecholamines is the α-blocker phenoxybenzamine (10–20 mg orally 3–4 times daily) because it is a non-competitive antagonist, unlike prazosin or doxazosin.

- If α-blockade produces a marked tachycardia, then a β-blocker such as propranolol can be added. On no account should a β-blocker be given before an α-blocker, as this may cause a paradoxical rise in blood pressure due to unopposed α-mediated vasoconstriction.

- After control of blood pressure the tumor is removed by surgery.
- During surgery, sodium nitroprusside and the short-acting α-antagonist phentolamine are useful in controlling hypertensive episodes, which may result from anaesthetic induction or tumour mobilisation.

Metastatic tumours may behave in an aggressive or a very indolent fashion. Management options include debulking surgery, radionuclide therapy with 131I-MIBG, chemotherapy and (chemo) embolisation of hepatic metastases; some may respond to tyrosine kinase and angiogenesis inhibitors.

THANKS