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Feature

Type XX (female) genotype XY (male) genotype • Hypotension 21β-hydroxylase deficiency • Clitoromegaly and/or male external genitalia along with a uterus and ovaries
• Precocious puberty
• Virilization, irregular menstrual cycles, infertility • Hypertension 11β-hydroxylase deficiency • Clitoromegaly and/or male external genitalia along with a uterus and ovaries
• Precocious puberty
• Virilization, irregular menstrual cycles, infertility • Hypertension 17α-hydroxylase deficiency • Normal female external genitalia at birth • Delayed puberty (primary amenorrhea) or sexual infantilism

Classical CAH (C-CAH) Nonclassical CAH (NC-CAH) • The sever form • The milder form • Less common • more common • Early onset (during the neonatal period or early infancy) • Females present with ambiguous genitalia.
• Salt-wasting type (~ 67% of all classic forms) → “adrenal crises” : vomiting and shock. • Non-salt-wasting type (simple virilizing, ~ 33% of all classic forms) → No signs of shock. • Males present with precocious puberty at age 2–4.

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• Hypotension • Normal male external genitalia at birth • Precocious puberty • Hypertension • Normal male external genitalia at birth • Precocious puberty • Hypertension • Female external genitalia with a blind-ending vagina and intra-abdominal testes at birth
• Delayed puberty or sexual infantilism • Late onset (manifests during late childhood, adolescence, or adulthood) • Normal external genitalia
• Symptoms of hyperandrogenism include hirsutism, acne, menstrual irregularity, androgenic alopecia, and impaired fertility

Chapter 1

Endocrinolog & Metabolism

• ACTH excess →hyperpigmentation (common feature in all forms of CAH) • Under- and over-treatment of CAH → Premature epiphyseal closure → short stature • Patients might complain of no

other symptoms apart from primary amenorrhoea. • The clinical presentation may be indistinguishable from polycystic ovarian syndrome, with hirsutism being a dominant feature.

Type 21β-hydroxylase deficiency Blood pressure Hypotension Hypertension Hypertension Acid-base disorders Metabolic acidosis Metabolic alkalosis Metabolic alkalosis 17-Hydroxyprogesterone Elevated
Elevated
Decreased
11-Deoxycorticosterone Decreased Elevated Elevated Corticosterone Decreased Decreased Elevated Potassium Elevated Decreased Decreased

Diagnosis • Screening is conducted by measuring 17-hydroxyprogesterone → elevated
 can help to distinguish between PCOS and non-classical CAH. • ACTH stimulation test (synacthen stimulation test) can diagnose 21-OH deficiency when the plasma 17-OH progesterone are more than 30 nmol/L.
 In individuals with borderline 17-hydroxyprogesterone levels, we recommend obtaining a complete adrenocortical profile after a cosyntropin stimulation test
• Genotyping only indicated when: results of the adrenocortical profile after a cosyntropin stimulation test are equivocal, or
 cosyntropin stimulation cannot be accurately performed (i.e., patient receiving glucocorticoid), or
 for purposes of genetic counseling. • Normal ultrasound scan will rules out other causes of primary amenorrhoea (Turner syndrome and testicular feminization).

Management
• Glucocorticoid replacement Hydrocortisone in neonates and children Prednisolone or dexamethasone in adolescents and adults steroids given in reverse circadian rhythm, i.e. a higher dosage at night and a lower dose in the morning (when steroids are given in higher doses at night → ACTH is suppressed → ↓ over-secretion of adrenal androgens and ↓the normal physiological steroid peak in the morning) • Symptomatic If the main concern is infertility, ovulation induction is the treatment of choice. If hirsutism is the presenting problem, then anti-androgens (such as flutamide) should be used. Notes & Notes for MRCP
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11β-hydroxylase 17α-hydroxylase deficiency deficiency

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• Restoring functional anatomy by surgery minimally virilized girls: surgical options, include delayed surgery and/ or observation until the child is older In severely virilized females (single urogenital opening) → early surgery to repair the urogenital sinus
• Specific treatment 21β-hydroxylase deficiency Lifelong fludrocortisone therapy (aldosterone substitution) Sodium chloride (salt) supplements, especially during infancy and childhood 11β-hydroxylase deficiency Spironolactone to block mineralocorticoid receptors Reduced dietary sodium intake 17α-hydroxylase deficiency Spironolactone to block mineralocorticoid receptors

 Estrogen replacement therapy for female genotype; may be started in early puberty Reduced dietary sodium intake Salt-wasting CAH Fluid resuscitation with intravenous normal saline Intravenous dextrose in patients with significant hypoglycemia Immediate administration of glucocorticoid replacement therapy Nonclassic CAH Women: combined oral contraceptives are first-line treatment (alternatively glucocorticoid therapy) Men: usually no treatment required Monitoring of treatment • Efficacy of treatment is best monitored by 17-OH progesterone and androstenedione levels
• Renin activity levels can be used to monitor the adequacy of mineralocorticoid and sodium replacement.

The dose of glucocorticoids must be increased during severe infection, critical illness, and perioperatively to meet increased demands to prevent adrenal crisis.

Glucocorticoid remediable aldosteronism (GRA)

GRA should be suspected as the cause of primary aldosteronism when there is a positive family history and the onset of hypertension is before age 21 years.

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Overview
• GRA is a rare subtype of primary aldosteronism, also called familial hyperaldosteronism (FH) type I • Autosomal dominant mutation leads to ACTH responsive aldosterone production from the zona fasciculata rather than the zona glomerulosa.
• It occurs because the regulatory portion of the 11b-OH gene binds to the aldosterone synthase gene. • usually associated with bilateral adrenal hyperplasia.

Features • Strong family history of early resistant hypertension and haemorrhagic strokes is characteristic. • Elevated plasma aldosterone and suppressed renin • Hypokalaemia potassium is normal in more than one-half of cases of GRA in contrast to the hypokalaemia frequently seen in primary aldosteronism.
• Markedly increased levels of 18-oxocortisol and 18-hydroxycortisol. • Responsive to corticosteroid therapy.

Complications
• increased risk ruptured intracranial aneurysms → hemorrhagic stroke (higher than that reported in autosomal dominant polycystic kidney disease.)

Diagnosis • dexamethasone suppression test • genetic testing (now preferred over dexamethasone suppression testing for making the diagnosis of GRA)

Treatment • physiologic doses of a glucocorticoid will correct the overproduction of aldosterone by suppressing ACTH.

The main clinical clues suggesting GRA in the normokalaemic, hypertensive patient are:

1. family history of hypertension
2. onset at a young age
3. frequent development of marked hypokalemia after the administration of a thiazide diuretic (which increases sodium delivery to the aldosterone-sensitive potassium secretory site in the cortical collecting tubule).

The combination of low renin, high aldosterone and raised urinary oxocortisol suggests glucocorticoid remediable aldosteronism (GRA).

GRA is autosomal dominant, and therefore genetic testing is the most appropriate investigation. (SCE-question samples-mrcpuk.org)

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Pseudohyperaldosteronism

Definition • Pseudohyperaldosteronism is characterized by a clinical picture of hyperaldosteronism with suppression of plasma renin activity and aldosterone.
Feature Hypertension Salt retention Hypokalaemia
 Low renin and aldosterone concentrations

Causes • Congenital adrenal hyperplasia • Exogenous mineralocorticoid • Cushing syndrome • Liddle syndrome • 11β-hydroxysteroid dehydrogenase deficiency • Glucocorticoid resistance • Excessive licorice ingestion: Excessive consumption of licorice can lead to inhibition of cortisol degradation → hypertension associated with hypokalemia.

Syndrome of Apparent Mineralocorticoid Excess (SAME)

Definition
• AME is a rare form of pseudohyperaldosteronism characterized by very early-onset and severe hypertension, associated with low renin levels and hypoaldosteronism. Causes • Congenital deficiency of 11-beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2) : Autosomal recessive mutation. • Acquired reduction of the activity of the (11 bHSD) enzyme caused by: carbenoxolone
 grapefruit juice ↑ liquorice consumption (glycyrrhizic acid): black substance produced from the root of a plant used in medicine and sweets) Pathophysiology
• With normal 11- beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2) activity: 11-beta-HSD2 converts cortisol into cortisone (cortisone, unlike cortisol, does not activate mineralocorticoid receptors). • With 11-beta-HSD2 deficiency (or inhibition): ↓ cortisol conversion to cortisone → ↑ cortisol → ↑ mineralocorticoid receptor activity.

Feature
• Hypertension

• Low birth weight • Failure to thrive • Muscle weakness • Polyuria and polydipsia due to nephrogenic diabetes insipidus • Renal failure • ↑ Ratio of free urinary cortisol (urinary tetrahydrocortisol) to free urinary cortisone. (AME patients create less cortisone)

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In Syndrome of Apparent Mineralocorticoid Excess, cortisol has the SAME action as aldosterone.

Differential diagnosis • differentiate between AME and Liddle's Syndrome by administering a potassium-sparing diuretic:
 Liddle's syndrome: only respond to a diuretic that binds the ENaC channel,
 AME: respond to a diuretic that binds to ENaC or mineralcorticoid receptor.

Treatment • Cessation of licorice ingestion • Spironolactone to decrease the mineralocorticoid effects • Thiazide in hypercalciuria or nephrocalcinosis • Corticosteroids: exogenous corticoids block ACTH and suppress the endogenous secretion of cortisol.

Spironolactone (an aldosterone receptor antagonist) is effective in treating the syndrome of apparent mineralocorticoid excess but not Liddle syndrome!

Phaeochromocytoma

Pheochromocytoma = Episodic hypertension

Pheochromocytoma is part of MEN II.

Definition • Phaeochromocytoma is a rare tumors arising from chromaffin cells of the adrenal medulla and secreting catecholamines. Notes & Notes for MRCP
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 Chromaffin cells are modified post-ganglionic sympathetic cells that release catecholamines after stimulation by pre-ganglionic sympathetics. Overview
• The majority of pheochromocytomas are benign, unilateral, catecholamine-producing tumors. • Tumors arise from chromaffin cells, which are derived from the neural crest. • Present in up to 1% of all hypertensive patients • The peak incidence is between ages 20 to 40. • Equal sex distribution • familial in 10% • bilateral in 10% • malignant in 10% • Localisation ~ 90% adrenal medulla (physiologically activated by acetylcholine)
 ~ 10% extra-adrenal in the sympathetic ganglia (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta) ~ 10% at multiple locations • 25% of pheochromocytomas are hereditary (germline mutations): Multiple endocrine neoplasia type 2 (MEN 2A, MEN 2B) Neurofibromatosis type 1 (NF1) Von Hippel-Lindau disease (VHL)

Features
• Episodic hypertension (around 90% of cases, may be sustained)
 Triggers for paroxysmal elevations in blood pressure: foods and beverages high in tyramine (e.g., red wine, aged cheese), surgery, pressure on the tumor (e.g., during massage), or certain drugs (e.g., beta blockers, MAOIs)
• Paroxysmal
 Throbbing headache (80%) the most common presenting feature Diaphoresis (60%) Palpitations, tachycardia (70%) Pallor
 Abdominal pain and nausea Anxiety • Weight loss due to increased basal metabolism • Hyperglycemia • Signs of polycythemia, if EPO is secreted • Other features consistent with associated familial disorders: MEN 2A: medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia MEN 2B: medullary thyroid cancer, pheochromocytoma, oral/intestinal neuromas, and marfanoid habitus NF1: cutaneous neurofibromas, cafe-au-lait spots, and Lisch nodules VHL: renal cell carcinoma, hemangioblastoma, angiomatosis, and pheochromocytoma

5 most important Problems (5 P's) of Pheochromocytoma: increased blood Pressure, head Pain (headache), Perspiration, Palpitations, and Pallor

Hypertensive crises can be triggered by palpation of the tumor on abdominal exam.

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Investigations • Plasma free metanephrines test The best initial test The most sensitive test • 24 hr urinary collection of metanephrines
 The most specific test (sensitivity 86%) False positive urinary metanephrines can occur as a result of:
 hypoglycaemia, stress, exercise, drugs such as methyldopa, dopamine agonists or ganglion-blocking antihypertensives, various foodstuffs including coffee, chocolate, bananas and citrus fruits.
 The presence of noradrenaline alone usually indicates an extra-adrenal tumour. Paragangliomas (exception—organ of Zuckerkandl) secrete noradrenaline only, as they lack PNMT. Phenylethanolamine-N-methyltransferase (PNMT) is necessary for methylation of noradrenaline to adrenaline and is cortisoldependent. Small adrenal tumours tend to produce more adrenaline whereas larger adrenal tumours produce more noradrenaline Tricyclic antidepressants and labetalol interfere with adrenaline measurements and should be stopped for 4 days Plasma and urinary methoxytyramine levels are indicators of malignancy and can show isolated increases in patients with 'biochemically negative' malignant • Clonidine suppression tests
 may be used to differentiate patients who have borderline catecholamine levels
 Clonidine 300 micrograms orally—failure of suppression of plasma catecholamines into the normal range at 120 and 180min is suggestive of a tumour • Genetic testing: if MEN2A, MEN2B, NF1, or VHL is suspected • Immunohistochemical staining: positive for chromogranin, synaptophysin, and NSE • Adrenal/abdominal CT or MRI (after positive biochemistry tests to localize tumor) The definitive methods for localisation MRI: unlike most other adrenal

tumours, demonstrates a distinctive ‘bright white’ signal on T2-weighted MRI.
• Meta-iodo-benzyl guanidine (MIBG) scanning demonstrates specific uptake in sites of sympathetic activity used in cases where a tumour is confirmed biochemically but cannot be identified on CT or MRI.
 Performed preoperatively to exclude multiple tumours. Phenoxybenzamine may lead to false –ve MIBG imaging, so these scans should be performed before commencing this drug where possible. • 18F fluorodopamine PET scanning is superior to MIBG in localizing metastatic disease.

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The image reveals a large left suprarenal mass. The appearances are typical of a which, unlike most other adrenal tumours, demonstrates a distinctive ‘bright white’ signal on T2-weighted MRI.

Management
• Initial management →The patient must be first stabilized with medical management: Alpha-blocker (e.g. phenoxybenzamine), should be given first, before a betablocker. beta-blocker (e.g. propranolol): Unopposed beta blockade should not be used in the management of phaeochromocytoma because of the risk of paradoxical increases in blood pressure

• Laparoscopic tumor resection (adrenalectomy): treatment of choice No-touch technique
 Open surgical resection is reserved for large or invasive tumors. Preoperative blood pressure management: combined alpha-adrenergic and beta-adrenergic blockade First, a non-selective irreversible alpha-blocker is given : Phenoxybenzamine blocks alpha-1 and alpha-2 adrenoceptors equally and irreversibly
 After sufficient alpha-adrenergic blockade, a beta-blocker may be started for additional blood pressure control and control of tachyarrhythmias.

Prognosis • benign phaeochromocytoma →The 5-year survival rate is 95%
• malignant phaeochromocytoma → The 5-year survival rate is 40% • Hypertension may persist in 25% patients who have undergone successful tumour removal. • SHB gene mutation patients are associated with a shorter survival.

Primary hypoadrenalism (Addison's disease)

Addison’s disease is associated with metabolic acidosis
Primary hypoadrenalism is diagnosed by a short synacthen test and a failure to increase cortisol levels to above 500nmol/L

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• Damage to the adrenal gland leads to the deficiency in all three hormones produced by the adrenal cortex: androgen, cortisol, and aldosterone. Clinical findings are noted after 90% of the

adrenal cortex has been destroyed. • Hypoaldosteronism → hypotension (hypotonic hyponatremia and volume contraction), hyperkalemia, metabolic acidosis • Hypoandrogenism → Loss of libido + Impaired spermatogenesis (in men) • Hypocortisolism leads to: ↑ ACTH → ↑ production of POMC (in order to increase ACTH production) → ↑ melanocyte-stimulating hormone (MSH) → hyperpigmentation of the skin (bronze skin) ↑ ADH level → retention of free water → dilutional hyponatremia
 ↓ Expression of enzymes involved in gluconeogenesis → ↓ rate of gluconeogenesis → hypoglycemia Lack of potentiation of catecholamines action → hypotension

Prevalence
• Prevalence is around 5 per 100,000. • There is a female: male preponderance of 2:1

Causes
• Autoimmune destruction of the adrenal glands the commonest cause of hypoadrenalism in developed countries (80% of cases) 70% of patients have circulating anti-adrenal antibodies. • Associated with other autoimmune conditions such as
 pernicious anaemia
 thyroid disease
 Type 1 diabetes Vitiligo Chronic active hepatitis. • Infectious (e.g. mycobacterial, fungal, HIV) Adrenal tuberculosis (15% of cases) the most common cause in developing countries. In case with high ESR, TB adrenalitis should be considered
 the best investigation → CT abdomen
 reversible with anti-tuberculosis medications if given at an early HIV: affect10% of patients with HIV, due to cytomegalovirus (CMV) Fungal: Histoplasmosis: A systemic fungal infection caused by Histoplasma Acute meningococcal sepsis due to Neisseria meningitidis → disseminated intravascular coagulation (DIC) → acute adrenal hemorrhage, also known as Waterhouse-Friderichsen syndrome. Neisseria meningitidis is a gram-negative diplococcus that grows on chocolate agar. purpuric rash classically appears on the trunk and extremities secondary to the DIC • Infiltration of the adrenal glands Tumors (adrenocortical tumors, lymphomas, metastatic carcinoma) Amyloidosis Hemochromatosis • Vascular (eg, hemorrhage, emboli, thrombus)

Pathophysiology

 Anti-phospholipid syndrome (Hughes' syndrome) → haemorrhage through adrenal vein thrombosis → adrenal infarction Anticoagulant overdose → bilateral hemorrhage in the adrenal glands → acute adrenal insufficiency. Flank pain, hypotension refractory to resuscitative efforts, and hypoglycemia indicate acute adrenal insufficiency due to heparin overdose. Traumatic, iatrogenic (eg, surgery) • Drugs-induced adrenal insufficiency → Cortisol synthesis inhibitors Antifungals: Ketoconazole, Fluconazole Antibiotics: Rifampin Antiepileptics: Phenytoin, Barbiturates

Thinning of pubic and axillary hair is seen in females with Addison's disease due to reduced production of testosterones from the adrenal gland 0BMost cases of adrenal insufficiency are subclinical and only become apparent during periods of stress (e.g., surgery, trauma, infections), when the cortisol requirement is higher!

Features

Hormonal changes Clinical features Laboratory findings Hypoaldosteronism
• Hypotension • Salt craving • Hyponatremia • Hyperkalemia • Normal anion gap metabolic acidosis Hypocortisolism • Gastrointestinal complaints (e.g., nausea, vomiting, diarrhea) • Weight loss, anorexia • Fatigue, lethargy, depression • Muscle aches • Weakness • Sugar cravings • Orthostatic hypotension Hypoandrogenism • Loss of libido • Loss of axillary and pubic hair Elevated ACTH • Hyperpigmentation of areas that are not normally exposed to sunlight (e.g., palmar creases, mucous membrane of the oral cavity) → pathognomonic

This patient has buccal pigmentation which raises the possibility of adrenal insufficiency

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• Hypoglycaemia
• Hyponatremia ↓ DHEA-S ↑ Melanocyte stimulating hormone (MSH))

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Investigations

• Routine laboratory studies AGB → Normal anion gap metabolic acidosis due to ↓ bicarbonate CBC → normocytic normochromic anaemia, eosinophilia, lymphocytosis Electrolytes → Na ↓, K ↑, Ca ↑ Blood glucose → Hypoglycemia • Endocrine studies: Use stepwise endocrine testing Morning cortisol level: initial test
 the diagnosis can be ruled out by a basal serum cortisol value in the upper end of the reference range or higher
 cortisol ˃ 500 nmol/l makes Addison's very unlikely < 100 nmol/l strongly suggest hypocortisolism. 100-500 nmol/l should prompt ACTH stimulation test to be performed Random cortisol levels are of limited value, as cortisol secretion varies diurnally and with physiological stress.
 Cortisol levels are influenced by cortisol-binding globulin (CBG) and albumin levels.
 Morning ACTH level: obtain if morning cortisol is low
 Primary adrenal insufficiency: elevated ACTH levels > 100 pg/mL Secondary/tertiary adrenal insufficiency: ACTH levels low to normal
 ACTH secretion is subject to diurnal variation, which is why a morning sample is desirable.
 Exogenous glucocorticoids (via any route) can suppress ACTH secretion through negative feedback.
 Standard-dose ACTH stimulation test (short Synacthen test, cosyntropin test): gold standard test to confirm the diagnosis of primary adrenal insufficiency Method Administration of 250 mcg exogenous ACTH to stimulate cortisol secretion Measurement of cortisol levels before and 30 and 60 minutes after injection Physiological response: exogenous ACTH → ↑ cortisol If a patient is on prednisone, prednisolone, or dexamethasone, temporarily switch them to

hydrocortisone and hold hydrocortisone 24 hours prior to testing. Interpretation In primary adrenal insufficiency: peak cortisol level < 18–20 µg/dL (< 500–550 nmol/L): no rise in cortisol level In secondary/tertiary adrenal insufficiency: usually a rise in cortisol > 18–20 µg/dL (> 500–550 nmol/L) Variant: low-dose (1 mcg) ACTH stimulation test Uses a smaller dose of exogenous ACTH and is thought to better mimic physiological conditions Studies show mixed results regarding its superiority to the standarddose test.

short Synacthen test is definitive diagnostic test

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• Adrenal autoantibodies: anti-21-hydroxylase: present in approximately 80% of cases. • Imaging CXR: Screen for tuberculosis if an infective cause is suspected. CT or MRI adrenal glands: Screen for adrenal hemorrhage and malignant or infiltrative disease.

Primary hypoadrenalism • hyperprolactinaemia is reported and is glucocorticoid-responsive. • High plasma renin and angiotensin II. • High ACTH • High lipotropin • High plasma vasopressin

Management
• Replacement therapy: Glucocorticoid → oral hydrocortisone. Usually given in 2 or 3 divided doses. Patients typically require 20-30 mg per day, with the majority given in the morning dose Medications and food interacting with hydrocortisone and cortisone acetate: Drugs that affect hydrocortisone metabolism: need to increase the dose: Anti-epilepsy/barbiturates, Antituberculosis
 Drugs that affect hydrocortisone metabolism: need to decrease the dose: Grapefruit juice, Liquorice Mineralocorticoid → fludrocortisone Drugs that affect fludrocortisone (need to be avoided): Diuretics, Acetozolamide, Carbenoxolone, liquorice, NSAIDS Drugs that affect fludrocortisone (need to increase the dose): Drospirenone- containing contraceptive Essential hypertension in a patient with PAI should be treated by adding a vasodilator, not by stopping the mineralocorticoid replacement, although a dose reduction should be considered.

• Patient education During travelling Patient’s with Addison's should be given a hydrocortisone injection kit when travelling to use it if unable to take oral hydrocortisone or vomiting. This can prevent Addisonian crisis
 During an intercurrent illness the glucocorticoid dose should be doubled If unable to take the normal oral hydrocortisone then the patient should be advised to take IM hydrocortisone to avoid adrenal crisis . This is why all patients with Addison's disease should have IM hydrocortisone for these situations. During shift work Patients who work night-time shifts will need to adjust their dose schedule according to the work pattern (e.g. 10 mg upon awakening before going to work, instead of taking the first dose at 07:00 h).doses should be taken from when waking Glucocorticoid therapy should ideally mimic endogenous cortisol rhythm with the lowest level at time of falling asleep and highest at waking.

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Endocrinolog & Metabolism When a patient shifts their daytime routine, such as working on night shifts or travelling, the patient should be advised to take their morning dose on waking and maintain the timing from there. During an event of increased activity: If significantly strenuous activity (e.g. marathon) double the dose of glucocorticoid and mineralocorticoids Mineralocorticoid therapy will be eventually required in adrenal insufficiency to counter intravascular volume depletion. It is important in the presence of increased fluid loss that the mineralocorticoid dose is adjusted. This is why doubling of the dose is advised.
 If the patient was just on hydrocortisone then no additional fludrocortisone would be needed.
 If less strenuous activity (such as a long hike, was planned)
 increasing the dose of hydrocortisone by 5-10mg would be reasonable, without any change in fludrocortisone. This change would also apply for any day that increased activity is planned for. During pregnancy The doses of neither of the medications (hydrocortisone and fludrocortisone) should be preemptively increased in the first trimester.
• A trial of dehydroepiandrosterone (DHEA) is recommended in women with primary adrenal insufficiency who have low libido, low energy levels, or depressive symptoms despite glucocorticoid and mineralocorticoid replacement.

Waterhouse-Frederickson syndrome
• adrenal failure due to bleeding into the adrenal glands (otherwise referred to as haemorrhagic adrenalitis) and is most commonly caused by meningococcal septicaemia.

May 2008 exam: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause? Dehydroepiandrosterone (DHEA) deficiency

Wolman’s syndrome is characterised by:

1. primary adrenal failure,
2. hepatosplenomegaly, and
3. steatorrhoea.

Addisonian crisis Signs/symptoms of Addisonian crisis Neurological Haemodynamic Biochemical • syncope • confusion • lethargy • convulsions • hypotension • hypothermia • hyponatraemia • hyperkalaemia • hypoglycaemia

A person with Addisons’ who vomits should take IM hydrocortisone until

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Management of Addisonian crisis (medical emergency) • Intravenous fluids 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic • I.V Corticosteroids In a patient without a previous diagnosis of adrenal insufficiency → IV dexamethasone, as this will not interfere with cortisol assays needed for a short synacthen test, unlike hydrocortisone. For patients with a previously known diagnosis of adrenal insufficiency → 100 mg IV hydrocortisone because diagnostic testing is not necessary. continue hydrocortisone 6 hourly until the patient is stable.
 Mineralocorticoid (fludrocortisone) administration is not necessary in the acute setting because high cortisol exerts weak mineralocorticoid action.

Secondary hypoadrenalism

Definition • Adrenal hypofunction due to a lack of adrenocorticotropic hormone (ACTH)

Pathophysiology
• ↓ ACTH → hypoandrogenism and hypocortisolism • Aldosterone synthesis is not affected (mineralocorticoid production is controlled by RAAS and angiotensin II, not by ACTH). • If ↓ ACTH induced by ↓ CRH, then it is called tertiary adrenal insufficiency (↓ CRH → ↓ ACTH).

Causes • Hypopituitarism: ↓ ACTH → ↓ endogenous cortisol Pituitary tumors Craniopharyngioma (in youngers) Irradiation • Conditions that decrease CRH production (tertiary adrenal insufficiency): ↓ CRH → ↓ ACTH → ↓ cortisol release The most common cause is sudden discontinuation of chronic glucocorticoid therapy
(e.g., infection, trauma, surgery) during prolonged glucocorticoid therapy Rarer causes include hypothalamic dysfunction (e.g., due to trauma, mass, haemorrhage, or anorexia).

Secondary and tertiary adrenal insufficiency are far more common than primary adrenal insufficiency

Feature
• Symptoms and signs are similar to those of Addison disease • Differentiating features include: Absence of hyperpigmentation because ACTH secretion is not increased. Absence of mineralocorticoid deficiency (Aldosterone synthesis is not affected) No dehydration or hypotension
long Synacthen test can be used to distinguish primary adrenal failure from secondary adrenal failure

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 Relatively normal electrolyte. Hyponatremia if it occurs, is due to increased vasopressin secretion → volume expansion → dilutional hyponatremia. Hyperkalemia is not present
 Associated features of underlying cause, e.g. visual field defects if pituitary tumour. Other endocrine deficiencies may manifest due to panhypopituitarism (↓thyroid and gonadal function and hypoglycemia). Adrenal crisis is likely if a patient is treated with thyroxine, without hydrocortisone replacement. Hypoglycemia is more common in secondary adrenal insufficiency.

Primary adrenal insufficiency → Pigments the skin.
Secondary adrenal insufficiency → Spares the skin.
Tertiary adrenal insufficiency is due to → Treatment (cortisol).

Diagnosis Confirmatory Serum Testing for Secondary Adrenal Insufficiency Test Result ACTH Low (< 5 pg/mL) Cortisol Low (< 5 µg/dL [138 nmol/L]) ACTH stimulation test (short Synacthen test) Normal or subnormal Prolonged (24-h) ACTH stimulation test (Long Synacthen test) Cortisol should

continue to rise for 24 h

• Long Synacthen test (prolonged ACTH stimulation test for 24 h)
 Aim:
 To diagnose secondary (or tertiary, ie, hypothalamic) adrenal insufficiency.
 Before the test: The simple short test is usually done initially, because a normal response obviates the need for further investigation. If short Synacthen test is subnormal (failure to respond to ACTH →↓ cortisol) and secondary adrenal insufficiency is suspected → do long Synacthen test Because pituitary failure may cause adrenal atrophy and hence failure to respond to ACTH, the patient may need to be primed with long-acting ACTH 1 mg IM once/day for 3 days before the ACTH stimulation test if pituitary disease is suspected. Method:
 Cosyntropin 1 mg IM is given, and cortisol is measured at intervals for 24 h, typically at 1, 6, 12, and 24 h.
 Interpretation: In primary adrenal failure: No significant cortisol rise. In secondary adrenal failure: gradually rises cortisol to a peak at 24 hours Prolonged stimulation of the adrenal glands by ACTH in the long Synacthen test → gradually rises cortisol to a peak at 24 hours → confirm the diagnosis of secondary adrenal failure.
 in some cases of long-standing adrenal atrophy due to secondary adrenal insufficiency, the adrenal glands will not respond even after 24 hours and will require several daily doses of depot Synacthen before an adrenal response is seen. • CT or MRI of the brain to rule out a pituitary tumor or pituitary atrophy.

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Corticosteroids

Mechanism of action • Corticosteroids are hydrophobic small molecules and thus freely pass through cell membranes. They bind to inactive cytosolic glucocorticoid receptors, which then translocate to the nucleus to act as nuclear transcription regulators.

Summary of effects of systemic corticosteroids • The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below: Minimal glucocorticoid activity, very high mineralocorticoid activity Glucocorticoid activity, high mineralocorticoid activity Predominant glucocorticoid activity, low mineralocorticoid activity Very high glucocorticoid activity, minimal mineralocorticoid activity Fludrocortisone Hydrocortisone Prednisolone Dexamethasone Betmethasone

Side-effects • Glucocorticoid side-effects endocrine: impaired glucose regulation,
 increased appetite/weight gain,
 hirsutism,
 hyperlipidaemia Cushing's syndrome: moon face, buffalo hump, striae musculoskeletal:
 osteoporosis,
 proximal myopathy,
 avascular necrosis of the femoral head immunosuppression:
 increased susceptibility to severe infection,

 reactivation of tuberculosis psychiatric: insomnia, mania, depression, psychosis gastrointestinal: peptic ulceration, acute pancreatitis ophthalmic: glaucoma, cataracts suppression of growth in children intracranial hypertension • Mineralocorticoid side-effects fluid retention hypertension The pathogenesis of corticosteroid induced osteoporosis is multifactorial:

1. Corticosteroids reduce osteoblastic activity, and the resulting osteoblast/osteoclast imbalance causes loss of bone.

2. Corticosteroids reduce intestinal calcium absorption and lower circulating sex steroid levels.
   Selected points on the use of corticosteroids: • patients on long-term steroids should have their doses doubled during intercurrent illness For milder concurrent illnesses oral prednisolone is usually doubled for a few days. For sever illness convert prednisolone temporarily to IV glucocorticoids, conventionally 50-100 mg of hydrocortisone six hourly. Mineralocorticoid dose is always left unchanged.
   • the BNF suggests gradual withdrawal of systemic corticosteroids if patients have: received more than 40mg prednisolone daily for more than one week, received more than 3 weeks treatment or recently received repeated courses • Low dose i.v hydrocortisone improve outcome in sepsis More recent randomised controlled trials have suggested that there is a benefit in sepsis when lower physiological doses of steroids are given. • Lactose-containing methylprednisolone preparations should not be used in patients with cows' milk allergy • Corticosteroids are recognised to inhibit osteoblast activity and increase osteoblast apoptosis. This is thought to be a more important component in bone loss with respect to steroid induced osteoporosis versus any effect on osteoclasts. • Whilst corticosteroids do increase osteoclast activity, it is thought to be their effect on osteoblast activity which has a greater impact on bone mineral density. Steroid induced hypogonadism • Body builders may be involved in the illicit use of anabolic and androgenic steroids. These results are consistent with ongoing use of androgens.
   • The hypogonadism, if persistent, may be treated with human chorionic gonadotropin.
   Relative potencies of the glucocorticoids
   • It is important to know the relative potencies of the glucocorticoids. • 1 mg prednisolone is equivalent to 4 mg of hydrocortisone
   • Dexamethasone for instance is roughly 30 times more potent than hydrocortisone.
   Steroid doses equivalence • 1mg prednisolone = 4mg hydrocortisone • 1mg dexamethasone = 7mg prednisolone • Dexamethasone is roughly 30 times more potent than hydrocortisone. Anabolic steroids • Anabolic steroids can be taken orally (eg stanozolol) or may have to be injected because of their high first-pass metabolism (eg testosterone enantate) • Among their many unwanted effects, they increase the risk of cardiovascular disease: blood pressure is elevated blood lipid profiles change, with increased LDL-cholesterol and decreased HDLcholesterol haematocrit is increased,

leading to a prothrombotic tendency, although there is a protective decrease in plasma fibrinogen concentrations with prolonged use Abuse of androgenic steroids
• The abuse of androgenic steroids amongst people who practise certain sports is quite common. • side effects
 Paranoid delusions aggressive behaviour. Other side effects of these illicit drugs include:

 Acne Gynaecomastia (also increase in breast cancer risk) Hypertension Hypercholesterolaemia, and Hepatic tumours.

Cushing's syndrome (Hypercortisolism) Pathological definition • Cushing's syndrome →hypercortisolism from any cause. • Cushing's disease → hypercortisolism caused by ACTH-secreting pituitary adenoma → the most common cause of Cushing's syndrome (75% of cases). Epidemiology • Commoner in ♀ (♀:♂, 3–15:1). • Age: most commonly, 20–40 years Causes • Exogenous (iatrogenic) Cushing syndrome Prolonged glucocorticoid therapy → hypercortisolism → decreased ACTH → bilateral adrenal atrophy Most common cause of hypercortisolism Dexamethasone poses a higher risk for development of iatrogenic Cushing disease. Shorter-acting agents, such as prednisone or hydrocortisone, are recommended alternatives. • Endogenous Cushing syndrome Primary hypercortisolism (ACTH-independent Cushing syndrome) (5–10%) Autonomous overproduction of cortisol by the adrenal gland → ACTH suppression → atrophy of the contralateral adrenal gland Adrenal adenomas Adrenal carcinoma: abnormal liver function tests (LFTs) suggest metastases. Adrenal hyperplasia Secondary hypercortisolism (ACTH-dependent Cushing syndrome) Pituitary ACTH production (Cushing disease) (~ 75%): Pituitary adenomas →ACTH secretion → bilateral adrenal gland hyperplasia Ectopic ACTH production (~ 15%) : Paraneoplastic syndrome (e.g. small cell lung cancer) → ↑ ACTH secretion → bilateral adrenal gland hyperplasia Small cell lung cancer accounts 50-75% of cases of ectopic ACTH Cushing's syndrome - hypokalaemic metabolic alkalosis The overnight dexamethasone suppression test is the best test to diagnosis Cushing's syndrome

Endocrinolog & Metabolism characteristically associated with very low potassium levels. weight loss suggests there is an underlying malignancy → ectopic ACTH Pseudo-Cushing's (Alcohol-induced Cushing's syndrome) • Obese alcoholic consumer → ↑CRH secretion or impaired hepatic metabolism of cortisol→ cushingoid appearance → Induce false positive dexamethasone suppression test or 24 hr urinary free cortisol • Investigations Midnight serum cortisol: The most appropriate next step in the investigation of alcoholic patient after confirming hypercortisolism The hallmark of true Cushing's syndrome is lack of diurnal variation in serum cortisol. However, in pseudo-Cushing's diurnal variation is normally maintained. Insulin stress test (insulin tolerance test) used to differentiate between true Cushing's and pseudo-Cushing's in pseudo-Cushing's the insulin tolerance test will demonstrate hypoglycaemia with a rise in ACTH and cortisol. In

Cushing's syndrome, this hypoglycaemia induced response is lost. contraindicated in epilepsy, ischaemic heart disease, or hypoadrenalism. Raised MCV may point to alcoholism • Management: promote weight loss, and strict control of alcohol intake. Usually mild and disappears rapidly during abstinence from alcohol. Features • Skin Thin, easily bruising with ecchymoses Cortisol breaks down proteins in bone and skin , so the free amino acids can be used to make sugar. This leads to bruising, striae, muscle wasting, and osteoporosis. Stretch marks (classically purple abdominal striae) Hirsutism, Acne: due to increased adrenal androgen levels Delayed wound healing Flushing of the face If secondary hypercortisolism: often hyperpigmentation (darkening of the skin due to an overproduction of melanin), especially in areas that are not normally exposed to the sun (e.g., palm creases, oral cavity) Caused by excessive ACTH production because melanocyte-stimulating hormone (MSH) is cleaved from the same precursor as ACTH called proopiomelanocortin (POMC) Not a feature of primary hypercortisolism • Neuropsychological: lethargy, depression, sleep disturbance, psychosis • Musculoskeletal Osteopenia, osteoporosis → pathological fractures, avascular necrosis of the femoral head , vertebral collapse Muscle atrophy/weakness (proximal myopathy)

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• Endocrine and metabolic Insulin resistance → hyperglycemia (see “Diabetes mellitus”) → mild polyuria in the case of severe hyperglycemia Dyslipidemia Fat redistribution: “moon face,” buffalo hump, truncal obesity, thin arms and legs ♂: Decreased libido ♀: Decreased libido, virilization, and/or irregular menstrual cycles (e.g., amenorrhea) • Other features Secondary hypertension (~ 90% of cases): due to fluid and sodium retention Increased susceptibility to infections (due to immunosuppression) Peptic ulcer disease Cataracts Most commonly → Posterior subcapsular cataract The predominant feature of a posterior subcapsular cataract is glare when looking into bright lights, either from the sun or car headlights. Menstrual irregularity is found in 84% of female patients with Cushing syndrome • General laboratory findings Hyperglycemia (Diabetes mellitus may occur in 30%): Cortisol → ↑gluconeogenesis (from protein break down → free amino acids) →↑glucose levels Hyperlipidemia Hypokalaemic Metabolic alkalosis: caused by increased urinary loss of H+ (acid) Leukocytosis Low oestradiol Diagnosis: confirm Cushing's syndrome (hypercortisolism) and then localise the lesion. • Tests to confirm Cushing's syndrome (hypercortisolism) : the two commonly used are:

1. Overnight low dose (1 mg) dexamethasone suppression test (ODST) Sensitivity and specificity are 98% (most sensitive) Low sensitivity and specificity in obese subjects (75-80%) therefor (UFC) will be best than (ODST) in obese If cortisol is suppressed → Cushing's disease is the likely cause. If cortisol is not suppressed → either primary adrenal Cushing's syndrome (low/undetectable ACTH) or ectopic ACTH is the cause (high ACTH). Causes of false-positive ODST (meaning that a diagnosis of Cushing is suggested incorrectly) cytochrome p450 inducers (Dexamethasone is metabolised by the cytochrome p450 system, specifically by the CYP3A4 isoenzyme). ↑oestrogen exposure (eg, pregnancy, oral contraceptives) →↑corticosteroid-binding globulin (CBG): need 6 weeks washout before the test If ODST is not offered in a question, then 24 hour urinary free cortisol is the next best answer
2. 24 hr urinary free cortisol (UFC) Can be useful for outpatient screening

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 Due to false –ve rate of 10% it should not be used alone. should be followed by an overnight dexamethasone suppression test. If both of these tests are normal, then Cushing syndrome could be ruled out. Factors lead to false +ves: Fenofibrate, carbamazepine, and digoxin.

• Tests to localise the lesion (source of the hypercortisolism):

1. The first step is to measure ACTH level: ACTH level low: This means the origin is in the adrenal gland → Scan the gland with a CT or MRI. ACTH level high: This means the origin is either in the pituitary gland or from the ectopic production of ACTH.
2. The next step is a high-dose (8 mg) dexamethasone suppression test (to differentiate between Cushing disease and ectopic ACTH production) If high-dose dexamethasone suppresses the ACTH → adequate suppression of cortisol levels to less than 50% of baseline: the origin is the pituitary. Scan the pituitary.
   If high-dose dexamethasone does not suppress the ACTH (No cortisol suppression): the origin is an ectopic production of ACTH or a cancer that is making ACTH. Scan the chest for lung cancer or carcinoid. Serum cortisol levels would remain unchanged with both lowlevel and high-level dexamethasone testing due to the lack of glucocorticoid receptors to facilitate negative feedback on the ectopic cells producing the ACTH. Anterior pituitary corticotrophs do have these receptors and, therefore, will be suppressed by any dose of dexamethasone. The use of high-dose dexamethasone suppression testing is an area of debate, owing to its variable sensitivity and specificity.
3. CRH stimulation test ACTH and cortisol levels increase further: Cushing disease No increase in ACTH or cortisol levels: ectopic ACTH production
4. Inferior Petrosal sinus sampling (IPSS) IPSS is the only test with sufficient diagnostic accuracy to differentiate Cushing's disease from ectopic ACTH production (the test of choice) Patient with high ACTH without definitive lesions on MRI should undergo IPSS: Up to 40% of patients with Cushing's disease will not have visible lesions on pituitary/sellar MRI. (The overall sensitivity of MRI to diagnose Cushing disease is only 60% to 70%.) It samples venous blood draining from the pituitary gland, using a femoral approach. A raised ACTH from here compared to the periphery suggests a pituitary cause.
   Patients with an IPSS central/peripheral gradient of ACTH ˃2:1 or 3:1 after corticotrophin-releasing hormone (CRH) stimulation → Cushing's disease
   Patients without high central/peripheral gradient of ACTH → ectopic ACTH → do CT of the chest, abdomen, and pelvis to look for a tumour secreting ACTH.
   The most common tumours that secrete ACTH are bronchial or thymic carcinoids.

Dexamethasone suppression tests
• The low-dose (1 mg) dexamethasone suppression test: used to confirm Cushing's syndrome (hypercortisolism) • The high-dose (8 mg) dexamethasone suppression test: used to differentiate between Cushing disease and ectopic ACTH production.

If a 24-hour urine free cortisol is elevated (one evidence of hypercortisolism), and there is an inadequate suppression on 1 mg overnight dexamethasone test (confirmatory test for hypercortisolism) in a patient suspected of Cushing syndrome, the next step would be to measure ACTH (to localise the lesion)

The following table summarizes the characteristics of the 3 sources of Cushing disease.

Pituitary Tumor Ectopic ACTH Production Adrenal Adenoma ACTH High High Low High-dose dexamethasone Suppression No suppression No suppression Specific test MRI, Petrosal vein sampling Scan chest and abdomen Scan adrenals
Treatment Removal

Which techniques is the best in differentiating between ectopic Cushing's syndrome and pituitary dependent Cushing's disease? Inferior petrosal sinus sampling
 The high-dose dexamethasone suppression test can differentiate between the two forms of Cushing's syndrome, but is not as accurate as inferior petrosal sinus sampling.

Which feature would favour benign adrenal adenoma as the cause of Cushing's syndrome over the other causes? Absence of hirsutism and virilisation (adrenal adenoma produces cortisol but not the androgens)

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Diagnostic steps in suspected Cushing's syndrome • Step 1 : Exclude exogenous corticosteroid use • Step 2 : Screen for hypercortisolism with 1 of the 4 high-sensitivity tests

1. late-night salivary cortisol;
2. 1 mg overnight low-dose dexamethasone suppression testing,
3. 24-hour urinary free cortisol; or
4. 48-hour 2 mg dexamethasone suppression testing. • Step 3: Exclude physiological causes of hypercortisolism (from history) physical stress, malnutrition, alcoholism, depression, pregnancy, class III obesity (BMI 40 or above) or metabolic syndrome. • Step 4: If an initial screening test is positive , and physiological causes of hypercortisolism have been excluded: confirm hypercortisolism with at least 1 additional test of the 4 highsensitivity tests. • Step 5: Once endogenous hypercortisolism is confirmed, plasma ACTH should be measured.
   If ACTH is suppressed, diagnostic testing should focus on the adrenal glands. → adrenal CT → adenoma. If ACTH is not suppressed, pituitary or ectopic disease should be sought.

Algorithm for the diagnosis of Cushing syndrome

In the diagnosis of hypercortisolism, hormone analysis always precedes imaging because microadenomas of the pituitary do not always appear upon imaging. Furthermore, imaging can reveal inactive adrenal tumors (incidentalomas) and pituitary tumors in many healthy individuals.

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Treatment • Fit for surgery Pituitary adenoma →Trans-sphenoidal hypophysectomy/adenomectomy is the initial treatment of choice.
 Adrenocortical tumor: laparoscopic or open adrenalectomy
 Laparoscopic adrenalectomy would be advised where pituitary surgery has failed. The recurrence rate for Cushing's disease after surgery is 20-30% and depends on the size of the tumour with macroadenomas having a higher rate of relapse. ACTH-secreting ectopic tumor: resection of the ectopic foci (e.g., bronchial carcinoid) • Unfit for surgery
 Ketoconazole may be an effective treatment for patients unfit for surgery Mitotane is an adrenolytic drug licensed for symptomatic treatment of advanced or inoperable adrenocortical carcinoma → improve the prognosis

Which drug is most appropriate to improve metabolic parameters prior to surgery in pituitary-dependent Cushing's? Metyrapone → inhibits 11-beta hydroxylase → inhibits cortisol production.

What is the optimum time for the administration of hydrocortisone to a patient undergoing bilateral adrenalectomy for Cushing's disease? Immediately following the removal of both adrenal glands.

Perioperative management of a cortisol producing adenoma includes:
• Peri and postoperative hydrocortisone with further assessment of postoperative cortisol secretion