

ENDOCRINOLOGY NOTES

PITUITARY DISORDERS

Growth Hormone usually decreases following an elevation in blood glucose after a meal. It is usually increased during sleep or during starvation. It causes both retention of sodium and potassium which are required for growth metabolism.

Elevated GH levels increase **IGF-1** blood levels. Because IGF-1 levels are much more stable over the course of the day, they are often a more practical and reliable measure than GH levels. Elevated IGF-1 levels almost always indicate acromegaly.

The **oral glucose tolerance test** is also used to diagnose acromegaly, because ingestion of 75 g of the sugar glucose lowers blood GH levels less than 2 ng/ml in healthy people. In patients with acromegaly, this reduction does not occur.

In **acromegaly**, hypertension, diabetes and goitre are associated. A damaged pituitary stalk reducing the dopamine suppression signal, stimulates prolactin secretion. Pseudogout (calcium pyrophosphate deposition) is also associated. Patients have normal calcium but increased phosphate levels. Patients with acromegaly have an increased risk of colorectal neoplasia.

The best treatment option for a large pituitary tumour in **acromegaly** is transphenoidal removal of the tumour. **Octreotide** (somatostatin analogue) and **pegvisomant** (growth hormone receptor blocker) are effective forms of treatment. **Bromocriptine** (dopamine agonist) is less effective.

Prolactin secretion is inhibited by dopaminergic pathway. **Hyperprolactinaemia** can be caused by Dopamine receptor antagonists (many antipsychotic drugs e.g. phenothiazines, risperidone), hypothyroidism, liver or renal failure, pituitary adenoma /acromegaly. It leads to galactorrhoea and osteoporosis/osteopenia. Treatment is with **dopamine receptor agonists** (bromocriptine, cabergoline).

Microprolactinoma: The most frequent symptoms at onset are oligoamenorrhoea (60%) and galactorrhoea (50%), and headaches. Treatment is with bromocriptine (e.g. 5 mg od).

Cushing's syndrome is a non-specific name for any source of excessive glucocorticoids. There are four main causes:

- 1) Exogenous glucocorticoids
- 2) Pituitary Cushing's syndrome known as **Cushing's disease**, due to a pituitary adenoma secreting excessive ACTH
- 3) Ectopic production of ACTH. Two varieties; one due to malignant tumours usually of the lung , these patients present with hypertension, hypokalaemia and hyperpigmentation. The second type is due to carcinoid tumours.

In the *dexamethasone suppression test* normal individuals suppress cortisol levels to < 50 nmol/L.

The **inferior petrosal sinus sampling** test, an elevated central ACTH concentration compared to a peripheral value (from arm veins) indicates **pituitary dependent Cushing's disease**. The test involves a microcatheter being advanced through initially the femoral vein and eventually into the inferior petrosal sinuses which lie along the internal aspect of the skull base which drain blood from the pituitary gland.

Metyrapone is an inhibitor of 11 beta hydroxylase, inhibiting the conversion of 11 deoxycortisol to cortisol, and can be used as treatment in Cushing's syndrome.

In **ectopic ACTH syndrome**, hypokalaemic alkalosis is typical. Ectopic ACTH is not suppressed by high doses of steroids such as 8 mg dexamethasone.

It is typically caused by *small cell carcinoma of the lung*. Thymoma, carcinoid tumour, medullary carcinoma of the thyroid, pancreatic carcinoma and phaeochromocytoma are associated with ectopic ACTH secretion.

Pituitary apoplexy is characterized by sudden onset of headache, visual symptoms, confusion and hormonal dysfunction due to acute hemorrhage or infarction of a pituitary gland. The pituitary gland is susceptible to infarction during *pregnancy* due to its increased size/blood flow. Hyponatraemia, hyperkalaemia and hypoglycaemia are as a result of secondary adrenal failure due to lack of ACTH.

Clomiphene is used as a fertility drug in hypopituitarism. It stimulates ovulation through the release of gonadotropins from the pituitary gland. It can also be used in PCOS and in treating male infertility.

DIABETES

A random glucose of >11.1 and a fasting glucose of >6.8 mmol/L (two occasions) would confirm the diagnosis .

Diabetic neuropathy

Autonomic neuropathy to the gut, bladder and sexual organs (impotence) can occur. A 3rd nerve mononeuropathy can occur. Motor neuropathy can cause muscle wasting, and sensory neuropathy causes vibration sensory loss.

In diabetic patients with microalbuminaemia demonstrated on urine dipstick, *ACE inhibitors* have been shown to reduce progression towards diabetic nephropathy.

Aggressive hypertension control is the best way of *preventing progression from microalbuminuria to macroalbuminuria*. Although glycaemic control is important, it is not as important as hypertensive control in preventing progression towards nephropathy.

According to **NICE guidelines**,
target of HbA1c is 6.5-7.5%,
BP target is 135/75,
albumin:creatinine target is ratio >2.5 (men) and >3.5 (women),
renal consult advised if creat >150, and
ACE inhibitor should be introduced to those with microalbuminuria.

In diabetics who have had an **MI**, the DIGAMI study showed that intravenous insulin for 24 hours and subcutaneous insulin for 3 months improved mortality rates for up to 3 years after.

Metformin is a biguanide. It improves insulin sensitivity and is helpful especially in patients who are overweight as it does not stimulate appetites in the way that sulphonylureas do.

Hyperosmolar non ketotic coma is characterised by markedly raised blood sugar, often >50 mmol/L. There is no significant ketosis and acidosis.

It occurs in patients with **Type 2 diabetes** of middle age or older. Treatment should be with isotonic saline, low dose insulin and potassium replacement.

Syndrome X describes a range of abnormalities often seen with insulin resistance. These include hyperinsulinaemia, hypertension, hypertriglycerides, low HDL and obesity.

THYROID DISORDERS

Clinical features of **hypothyroidism** are cold intolerance, constipation, menorrhagia, angina, myxoedematous facies, dry rough skin due to mucopolysaccharidoses, hair loss, hoarse voice, dementia, cerebellar ataxia, peripheral neuropathy and depressed reflexes.

Recognised features of **thyrotoxicosis** are: Weight loss, Palpitations, Dyspnoea, Irritability, Psychosis, Tremor, Pruritus, Diarrhoea, Palmar erythema, Hypercalcaemia, Hyper-reflexia, Bone mineral loss and Alopecia.

Graves disease is the diagnosis - thyroid autoantibodies are increased. Almost 80% of patients have exophthalmos. Medical treatment such as carbimazole or radioiodine treatment are recommended rather than surgery. There will be increased uptake on the thyroid radioisotope scan.

Toxic thyroid nodules are best treated with radioactive iodine as this concentrates on the overactive adenoma cells. Radioiodine treatment is contraindicated in young children, pregnant and lactating women. The major complication of treatment with **radioactive iodine** is the progressive incidence of *hypothyroidism* and thyroid replacement may be necessary in the future.

The appropriate initial treatment of **Amiodarone induced hyperthyroidism** would be carbimazole +/- steroids.

Subacute thyroiditis (De Quervain's thyroiditis) is a transient thyroditis which is thought to be of viral aetiology. There is a swollen painful thyroid gland with hyperthyroidism. This is usually followed by a period of hypothyroidism with raised TSH weeks later. Antithyroid medication is not effective. Steroids can be used in severe cases.

Hashimoto's thyroiditis. This disorder occurs most commonly in middle-aged women and is caused by the reaction of the immune system against the thyroid gland. It may occur in people with a family history of thyroid diseases or with other autoimmune diseases, especially type 1 diabetes or adrenal insufficiency.

Sick euthyroid is seen in unwell patients who are clinically euthyroid but have low levels of T3 and T4. The syndrome is very common and, in fact, may be found in up to 70% of hospitalized patients. This is often why TFT's are not accurate on patients in ITU.

The rare syndrome of **resistance to thyroid hormone** (RTH) is an inherited disorder called **Refetoff syndrome** that involves reduced tissue sensitivity to the thyroid hormone.

Calcitonin is secreted by thyroid cells. Its release is stimulated by a high calcium level. Bone cells lay down calcium in response to calcitonin, and hence it is used as a treatment for osteoporosis. Calcitonin also stimulates renal excretion of calcium.

THYROID CARCINOMA

Medullary thyroid carcinoma produces peptides and neurohormones which lead to symptoms of irritability, diarrhoea and sweating. It can be inherited in association with MEN type II.

Anaplastic thyroid carcinoma is commoner in female patients. It can present with dysphagia, cough and neck pain. It is more invasive than papillary carcinoma.

Poor prognostic factors in thyroid carcinoma include advanced age (>50), male, advanced stage, prior neck surgery, and associated multiple endocrine neoplasia. Overall, papillary carcinoma has a 30-year cancer-related death rate of 6%. Follicular carcinoma has a 30-year cancer-related death rate of 15%.

PARATHYROID DISORDERS

Parathyroid hormone levels rise with hypocalcaemia. It increases plasma calcium by:
increasing osteoclastic resorption of bone (rapid effect)
increasing intestinal absorption of calcium (slow effect)
an increase in tubular resorption of calcium and increased excretion of phosphate

Primary hyperparathyroidism. The radiograph of the skull commonly shows osteopenia with a speckled appearance - the so called "pepper pot skull". In **primary hyperparathyroidism**, typically there is hypercalcaemia, low phosphate and raised alkaline phosphatase.

Causes of hyperparathyroidism are:
1. Diffuse hyperplasia 10-40%
2. Single adenoma 50-80%
3. Multiple adenomas 10%.
4. Parathyroid Carcinoma 2%

Pseudohypoparathyroidism is a genetic disorder that resembles hypoparathyroidism (lowered levels of parathyroid hormone) but is caused by a lack of response to parathyroid hormone rather than a deficiency in the hormone itself. A picture very similar to hypoparathyroidism develops with hypocalcaemia in the blood and high phosphate levels.

This defect also causes short stature, round face and short hand bones and is also called Albright's hereditary osteodystrophy. When Albright's hereditary osteodystrophy occurs without hypocalcemia, it is known as **pseudopseudohypoparathyroidism**.

DiGeorge syndrome is a cause of **hypoparathyroidism**. The disorder is associated with thymic aplasia, immune deficiency and cardiac anomalies (tetralogy of Fallot VSD, ASD).

MULTIPLE ENDOCRINE DISORDERS

MEN 1 [pituitary tumour, parathyroid hyperplasia/tumour, pancreatic tumours (most commonly gastrinoma / insulinoma)]. Also known as Wermer's syndrome.

Hyperparathyroidism is the most common and earliest feature of MEN1 (80-95%). Usually all four glands become hyperplastic.

Neoplastic transformation of pancreatic islets is the second most common manifestation of MEN1 (80%). Gastrinomas are the most common (presenting with peptic ulcer disease and diarrhoea). Insulinomas are the second most common. Pituitary tumours occur in 50-70% of cases.

Familial multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder. The MEN1 gene on chromosome 11q13 has been cloned and mutations identified. The gene encodes a protein called menin which acts as a tumour suppressor gene.

MEN 2

MEN 2a is associated with medullary thyroid carcinoma (MTC), parathyroid tumours (10-20%) and pheochromocytoma (20-50%).

MEN 2b is associated with presentation of medullary thyroid carcinoma, parathyroid tumours and pheochromocytoma + ganglioneuromatosis (pathognomonic), and marfanoid habitus.

ADRENAL DISEASES

Insulinoma: Hypoglycaemic attacks are likely to be witnessed during a 72 hour fast which is used to make the diagnosis. Insulin and C peptide levels are high, whilst glucose is low.

In **Conn's syndrome**, renin levels are low, and excretion of potassium is high due to increased sodium retention. There is autonomous *aldosterone* secretion in the presence of low or suppressed renin activity. A low potassium (< 3.5 mmol/L) accompanied by metabolic alkalosis is characteristic.

Adrenal adenoma is the commonest cause of Conn's syndrome. *Sodium chloride infusion* is a diagnostic test, aldosterone levels are suppressed in the normal population but not in Conn's syndrome patients.

Autoantibodies against *21-hydroxylase* (P450c21) are common in **Addison's disease**. Granulomatous, lymphocytic inflammation of adrenal glands occurs in autoimmune adrenalitis. There is also a genetic predisposition in those with HLA-B8, HLA-DR3, HLA-DR4 haplotypes.

Addison's disease as suggested by hyperpigmentation, hyponatraemia and hypotension. A high *9 am* plasma ACTH level with low or normal cortisol will confirm the diagnosis of primary hypoadrenalinism. A low cortisol response with the short ACTH (synacthen) test would also show that the adrenal gland is not responding to ACTH.

Associations with **Addison's disease**:

- pernicious anaemia
- primary ovarian failure
- vitiligo
- diabetes

The **short synacthen test** is done via the following:

- 1) take a basal sample for cortisol at time 0 min.
- 2) give 250 microgramme Synacthen i.v. or i.m.
- 3) sample for cortisol are taken at 30 mins. There should be a significant response unless the patient is addisonian.

Steroid replacement is usually given 10/5/5 mg or 10/5 mg, although this is adjusted with cortisol day curves. Fludrocortisone 100 µg mane should be adequate.

Steroids:

The equivalent ratio of prednisolone: hydrocortisone is 1:4.

The ratio for dexamethasone : prednisolone is 1:10.

The ratio for dexamethasone: hydrocortisone is 1:40.

Waterhouse-Friderichson syndrome is due to meningococcal septicaemia resulting in adrenal haemorrhagic insufficiency. Symptoms and signs include hypotension, abdominal pain, hyponatremia. The progression is rapid. There may also be disseminated intravascular coagulation in patients with this syndrome. If this condition is not treated promptly then mortality approaches 100%.

The treatment is as that for meningococcal infection, but with the addition of adrenal support with hydrocortisone, given intravenously in a dose of 200 mg per four hours.

Kallman's syndrome describes the occurrence of *hypothalamic gonadotrophin releasing hormone deficiency* and deficient olfactory sense - *anosmia*. It is usually inherited as an *X-linked or autosomal recessive* disorder with greater penetrance in the male. More than half of patients have associated nerve deafness, colour blindness,

mid-line crano-facial deformities such as cleft palate or harelip, and renal abnormalities. Most are of normal or above average stature. Females may present with primary amenorrhoea; males with cryptorchidism. LH and FSH levels are typically low.

Klinefelter's syndrome is the most common cause of male hypogonadism with an incidence of 1 in 1000 male births. Individuals have an extra X chromosome. Usually, the karyotype is 47, XXY. Accelerated atrophy of germ cells before puberty results in sterility with small, firm testes. Many patients are tall with relatively long legs. Behavioural disorders and delayed speech development are common. Testosterone therapy may be used to improve the development of secondary sexual characteristics.

Testicular feminisation is a cause of primary amenorrhoea rather than secondary amenorrhoea. Androgen insensitivity syndrome (AIS), formerly known as testicular feminization, is an X-linked recessive condition resulting in a failure of normal masculinization of the external genitalia in chromosomally male individuals.

Most patients with complete androgen insensitivity have a female gender. Some patients are first seen in the teenage years for evaluation of *primary amenorrhea*, but most are identified in the newborn period by the presence of *inguinal masses*, which later are identified as testes during surgery.

Vasopressin (Anti Diuretic Hormone) acts on the distal tubule and collecting ducts to increase permeability to free water. Deficiency of this hormone in **diabetes insipidus** results in the excretion of dilute urine (increased water clearance) and hypernatraemia.

In a *normal* response to the **water deprivation test** the maximum urine osmolality exceeds plasma osmolality and the urine osmolality does not increase > 5 % after administration of vasopressin. The *plasma osmolality* normal range is 278-300 mosmol/kg and *urine osmolality* normal range is 350-1000 mosmol/kg.

In **diabetes insipidus**, patients are unable to concentrate their urine to greater than plasma osmolality but after administration of vasopressin the urine osmolality increases by > 50 %.

Patients with **nephrogenic diabetes insipidus** are unable to concentrate their urine and they show no response to vasopressin

In **psychogenic diabetes insipidus** or compulsive water drinking, fluid deprivation would stop the polyuria. Plasma and urine osmolality (<300 msom/kg) should be low in psychogenic diabetes insipidus.

SIADH is confirmed by inappropriately elevated urine osmolality (often above 300 mOsm/kg) and urine sodium concentration (usually above 40 mEq/liter).

Phaeochromocytoma is a tumour of the adrenal medulla. The adrenal cortex produces aldosterone, cortisol (glucocorticoid) and adrenal androgens. The medulla produces adrenaline and noradrenaline. Phaeochromocytoma is associated with MEN II and von Hippel Lindau syndrome. There is an association with retinal, cerebral and

renal haemangiomas. Diagnosis is with raised urinary catecholamines over 24 hours, and also MIBG scan of the adrenals.

The treatment of hypertension in **phaeochromocytoma** is with alpha blockade prior to beta blockade. Alpha blockade reverses the peripheral vasoconstriction whereas beta blockade prevents tachycardia. The preferred alpha-blocker *phenoxybenzamine*, as it is not a selective alpha 1 blocker but an irreversible alpha-blocker whose effects cannot be overcome by an increase of catecholamines. Hypertension should be managed with phenoxybenzamine initially, increasing up to 80 mg per day, with addition of propanolol after 3-4 days of alpha blockade. Surgery without adequate alpha and beta blockade can result in hypertensive crisis (leading to high CVA, MI complications).

Polycystic Ovarian Syndrome (PCOS) is characterized by irregular ovulation and menses, obesity, insulin resistance, acne, and hirsutism (excessive hair growth). Impaired fertility is a prominent feature of PCOS. This is believed to result from elevated insulin levels that stimulate excess androgen production by the ovaries.

Biochemically, **PCOS** is associated with:
a raised LH:FSH ratio
insulin resistance
hyperandrogenism (raised androstenedione levels and raised testosterone).

Rapid development of hirsutism is usually caused by an **adrenal tumour**. There are high testosterone or DHEA levels in the plasma.

Causes of **hirsutism** include:
cyclosporin A
Risperidone
Minoxidil
Phenytoin
Ovarian tumours
Polycystic Ovary syndrome
Congenital adrenal hyperplasia

Alopecia is associated with
SLE
hypopituitarism
zinc and iron deficiency
hyper and hypothyroidism

Hyperpigmentation is associated with
pellagra
porphyria cutanea tarda
Nelson's syndrome
Haemochromatosis
Addison's disease
Whipple's disease
primary biliary cirrhosis.

Congenital adrenal hyperplasia: Hirsutism, ambiguous genitalia and precocious puberty in boys (normal puberty is seen in girls). Premature epiphyseal closure is a classical feature of CAH. It is also associated with hyperpigmentation and hyperreninaemia due to sodium loss and hypovolaemia.

21-hydroxylase deficiency is the commonest cause of congenital adrenal hyperplasia. This leads to excess androgen production due to shunting of *17 OH progesterone* into *testosterone and androstenedione* production. Increased 17 (OH) progesterone or pregnanetriol in the urine is diagnostic of 21 hydroxylase deficiency.

Virilisation may result in clitoromegaly and labial fusion in the female at birth.

11-beta-hydroxylase is the second most common variant of CAH and accounts for approximately 5% of cases. Deficiency of 11 beta-hydroxylase results in a loss of cortisol; hence, due to feedback mechanisms, there is an increase in ACTH and a subsequent increase in production of 11-deoxycorticosterone. Diagnosis is made by measuring *11-deoxycortisol*, which is typically high. In the classic form, other hormones that may be elevated include DOC (a potent mineralocorticoid), urinary 17-ketosteroids, and urinary tetra hydrometabolites.

Congenital Adrenal Hyperplasia : There is also cortisol deficiency and replacement with dexamethasone or hydrocortisone is appropriate. Efficacy of treatment is best monitored by 17OH progesterone and androstenedione levels. Renin activity levels can be used monitor adequacy of mineralocorticoid replacement. Hypertension and hypokalaemia suggest excess treatment.

Alkaptonuria is an autosomal recessive disease due to deficiency of the homogentisate oxidase enzyme. It causes accumulation of *homogentisic acid* which deposits in cartilage and connective tissue (causing sacroiliac joint and knee pains). It is one of the causes of pseudogout. Oxidation of homogentisate causes urine to turn dark on standing.

Familial hypocalciuric hypercalcaemia is an autosomal dominant disease. The pathophysiology is due to a defective calcium receptor on the membranes of the parathyroid and renal tubular cells. This results in a decreased renal clearance of calcium, PTH is usually normal or increased, PO₄ is usually decreased. Diagnosis is made on family history and determination of low urinary calcium clearance. Typically, the Fractional Excretion of Ca is <1%.

Haematin causes suppression of δ-aminolaevulinic acid (ALA) synthetase activity results in decreased production of ALA and prohobilinogen (PBG).

PORPHYRIA

Infection, pregnancy, stress (eg argument) and drugs can precipitate an **acute porphyria attack**.

Common drugs which can **precipitate a porphyria attack** are:

Barbiturates

Sulfonamides

chloroquine
steroids

Drugs which are **safe in porphyria** are:

Aspirin
Atropine
Glucocorticoids
Insulin
Narcotic analgesics
Phenothiazines
Ranitidine
Serotonin Reuptake Inhibitors (anti-depressants)
Streptomycin

Acute intermittent porphyria is a autosomal dominant disorder caused by a defect in *porphobilinogen deaminase activity*. If peripheral neuropathy, such as pain in the back and legs or parathesias occurs it is almost always preceded by abdominal pain. The defect in porphobilinogen deaminase causes a build up of ALA and porphobilinogen (PBG) which causes their increased secretion in the urine. **Urine PBG** is raised in acute intermittent porphyria, and the urine typically turns a red brown/ red colour on standing.

Hereditary coproporphyria (HCP) and **Variegate porphyria** (VP) have skin manifestations and acute attacks.

In **variegate porphyria**, there is increased production of protoporphyrinogens due to a mutation in protoporphyrinogen oxidase in the haem synthesis pathway. *Urinary porphobilinogen* is usually normal, unlike acute intermittent porphyria. Variegate porphyria is associated with intermittent abdominal pain, mood disturbances, and a bullous eruption that occurs over sun-exposed areas.

Acute attacks do not occur with **Porphyria cutanea tarda** (PCT).

Purpuric rash is the most common presenting feature of **cryoglobulinaemia** but other cutaneous features which may occur are Raynaud's phenomenon, telangiectasiae, urticaria and pigmentation.

Hypokalaemic periodic paralysis is a condition associated with hypokalaemia and episodes of weakness which may be profound. The weakness does not usually involve bulbar and respiratory function.

This disorder is commonly caused by medication, especially diuretics. Potassium should be given before bicarbonate as bicarbonate can precipitate further hypokalaemia. Other ways of preventing acute exacerbations are avoiding heavy carbohydrate meals, a very low sodium diet and spironolactone.

Abetalipoproteinaemia is a disorder in the synthesis of serum lipoproteins containing apolipoprotein B, for example chylomicrons, VLDL and LDL. It is a slowly progressive disorder characterised by:

retinitis pigmentosa
ataxia
areflexia

steatorrhoea
motor tics
emotional lability, but normal cognitive function

Phenylketonuria occurs due to a defective enzyme *phenylalanine hydroxylase*. Classic PKU is present when plasma phenylalanine levels accumulate and exceed 20 mg/dL (1200 mmol/L). Urinary phenylalanine metabolites are raised.

Phenylalanine accumulation causes severe low IQ, microcephaly, epilepsy, depigmentation of the iris and hair. Guthrie bacterial inhibition test is used for infant testing. Fe chloride turns green in urine due to ketones.

METABOLIC DISORDERS

Severe **hyponatraemia** can cause seizures, obtundation/decreased conscious level, headaches, upper motor neuron signs (central pontine myelinolysis), bradycardia (not tachycardia), hypotension and mydriasis.

Causes of hypomagnesaemia:

Loop diuretics
Aminoglycosides
Cyclosporine
amphotericin
cisplatin

Common causes of **rhabdomyolysis** are:

Alcohol
barbiturates
heroin overdoses
metabolic disorders (DKA, HONK, hyponatraemia, hypokalaemia, hypothyroidism).

Normal anion gap metabolic acidosis: The normal anion gap is 8-16. The anion gap in this question is $\text{Na}^+ + \text{K}^- - (\text{Cl}^- + \text{HCO}_3^-)$.

The causes of a **normal anion gap metabolic acidosis** are
renal tubular acidosis,
ileal conduit,
carbonic anhydrase inhibitors,
ammonium chloride ingestion.
Ureterosigmoidostomy

The causes of a **increased anion gap metabolic acidosis** are
toxicity with salicylates
ethylene glycol
toluene
lactic acidosis
diabetic ketoacidosis

Nephrocalcinosis is related to **type I (distal) renal tubular acidosis**. It also causes hyperchloraemic metabolic acidosis (it is one of the causes of normal anion gap metabolic acidosis).

Type II (proximal) renal tubular acidosis is typically related to a Fanconi syndrome (loss of amino acids, glucose, phosphate and uric acid into the urine).

Type 4 RTA is caused by a defect in the distal tubule, but it is different from classic distal RTA and proximal RTA because it results in hyperkalaemia rather than hypokalaemia. RTA type 4 is in effect hyporeninaemic hypoaldosteronism.

It occurs when blood levels of aldosterone are low or when the kidneys do not respond to it. Fludrocortisone is usually effective as a form of treatment.

Type IV RTA may result from sickle cell disease, urinary tract obstruction, lupus, amyloidosis, or transplantation.

Liddle's syndrome is an autosomal dominant condition leading towards increased renal tubular (collecting tubule) resorption of Na and in most cases potassium loss. There are classically *low renin and aldosterone levels* and normal cortisol levels. The cause is increased activity of luminal membrane Na channels. Treatment is with triamterene or amiloride.

Bartter's syndrome is an autosomal recessive renal disorder. Presentation is often in childhood with gastrointestinal upset and polyuria. There is associated hypokalaemic alkalosis, elevated renin and aldosterone levels. Vomiting, constipation, polyuria and polydipsia are common symptoms.