Pseudohypoadrenalism

- Pseudohypoaldosteronism type 1 usually presents in infancy with failure to thrive and salt wasting associated with hypotension, hyperkalaemia and large elevations in plasma renin and aldosterone.
- Defects are either in the epithelial sodium channel or in the mineralocorticoid receptor.
- Treatment is with a high sodium diet and high-dose fludrocortisone or carbenoxolone
- . Pseudohypoaldosteronism type 2 is an autosomal dominant condition typified by hyperkalaemia, hypertension and a mild hyperchloraemic acidosis. There is a mutation in the distal tubule chloride channel, resulting in enhanced distal chloride reabsorption in preference to excretion of potassium.
- Treatment is with a low-potassium diet and a thiazide diuretic.

Secondary adrenal hypofunction (adrenocorticotrophic hormone deficiency)

ACTH release may be impaired by disorders of the hypothalamus or the anterior pituitary gland, most commonly due to a tumour or infarction.

Corticosteroids suppress ACTH release and, if such drugs have been taken for a long time, the ACTH-releasing mechanism may be slow to recover after the steroid is stopped.

There may be temporary adrenal atrophy after prolonged lack of stimulation.

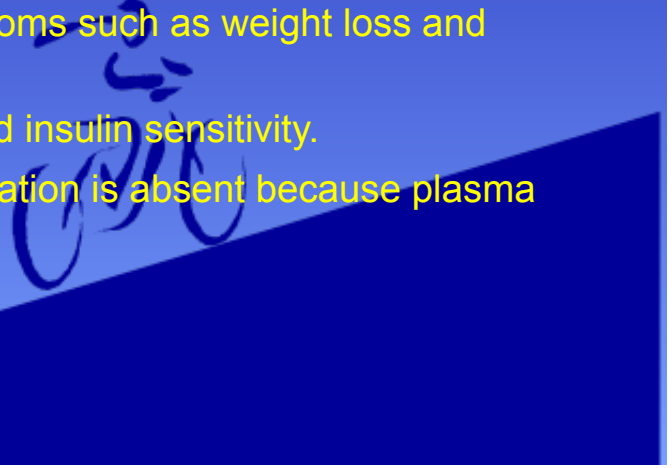
Adrenocortical deficiency may then only become clinically evident under conditions of stress, which may precipitate acute adrenal insufficiency.

The most common causes of stress are infection and surgery.

Patients may present with non-specific symptoms such as weight loss and tiredness.

Hypoglycaemia may occur because of marked insulin sensitivity.

Unlike primary adrenal hypofunction, pigmentation is absent because plasma ACTH concentrations are not raised.



INVESTIGATION OF SUSPECTED ADRENAL HYPOFUNCTION

- If a diagnosis of acute adrenal insufficiency is suspected clinically, blood should be taken so that the plasma cortisol concentration can be measured later; steroid treatment must be started immediately, as the condition can be life threatening.
- Adrenocorticol hypofunction may not be excluded on the results of a random plasma cortisol concentration,
- . Nor will plasma cortisol estimation distinguish between primary and secondary adrenal failure.
- The tetracosactide (Synacthen) stimulation test should be performed as soon as possible.
- Tetracosactide has the same biological action as ACTH but, because it lacks the antigenic part of the molecule, there is much less danger of an allergic reaction.

- A plasma autoantibody screen including adrenal antibodies may point to a primary adrenal autoimmune problem.
- Plasma ACTH assay may be of value when inappropriately low plasma cortisol concentrations have been found; a raised plasma ACTH concentration indicates primary insufficiency, whereas a low ACTH concentration suggests secondary insufficiency.
- The essential abnormality in adrenocortical hypofunction is that the adrenal gland cannot adequately increase cortisol secretion in response to stress.
- . Insulin-induced hypoglycaemia normally causes ACTH secretion from the anterior pituitary gland.
- This can be assessed by demonstrating a rise in plasma cortisol concentrations.
- An impaired response indicates pituitary dysfunction only if the adrenal cortices have already been shown to be capable of responding to exogenous ACTH.

- Suspected Addisonian crisis (acute)
- Before starting treatment, take blood for immediate plasma urea, creatinine and electrolyte estimations as well as plasma glucose, calcium and cortisol.
- Hyponatraemia, hyperkalaemia, hypoglycaemia and uraemia are compatible with an Addisonian crisis. Hypercalcaemia may also occur.
- Start steroid treatment once blood has been taken, as the condition is life threatening.
- If the plasma cortisol is very high, an Addisonian crisis is unlikely.
- Conversely, if the plasma cortisol concentration is very low , and if there is no reason to CBG deficiency, for example due to the nephrotic syndrome, an Addisonian crisis is likely. Plasma cortisol concentrations, which would be normal under basal conditions, may be inappropriately low for the degree of stress. To confirm this, perform a short Synacthen test

Suspected chronic adrenal hypofunction

Measure the plasma cortisol concentration at 09.00 h. If more than 580 nmol/L, Addison's disease is unlikely

If the plasma cortisol concentrations are equivocal, perform a short Synacthen test. A normal result makes long-standing secondary adrenal insufficiency unlikely.

insensitivity to trophic stimulation. Send a blood specimen for plasma ACTH.

If the plasma ACTH concentration is high, this confirms primary adrenal hypofunction.

A low ACTH concentration suggests secondary adrenal hypofunction, and pituitary assessment is indicated.

If the diagnosis is still unclear, admit the patient to a hospital and perform a prolonged Synacthen test.

A normal result excludes primary adrenal hypofunction.

An increasing response over time to the short and prolonged Synacthen tests indicates gradual recovery of the adrenal cortex and suggests hypothalamic or pituitary hypofunction.

Tetracosactide (Synacthen) test of adrenal function

Procedure

The patient should be resting quietly but not fasting.

It is recommended that the test is done in the morning.

Resuscitation facilities should be available in case of an allergic reaction.

Blood is taken for basal cortisol assay.

Synacthen 250 µg is given by intramuscular or intravenous injection.

Blood is taken for cortisol assay at baseline, 30 and 60 min.

Interpretation

Normally the plasma cortisol concentration increases by at least 200 nmol/L, to a concentration of at least 580 nmol/L.

The peak is usually at 30 min, although a steady increase at 60 min may imply secondary hypoadrenalism due to pituitary or hypothalamic disease.

Depot or prolonged Synacthen stimulation test

- Repeated injections of depot Synacthen are painful and may cause sodium and water retention.

- . Therefore this test is contraindicated in patients in whom sodium retention may be dangerous, such as those with congestive cardiac failure.

- Its main indication is to differentiate primary from secondary adrenal insufficiency.

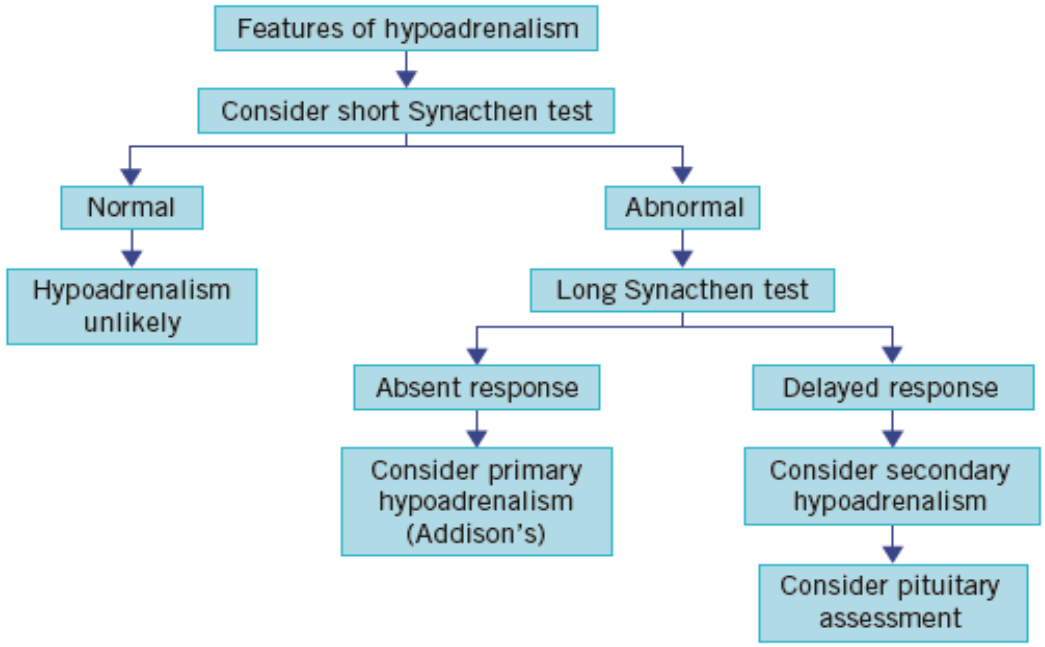
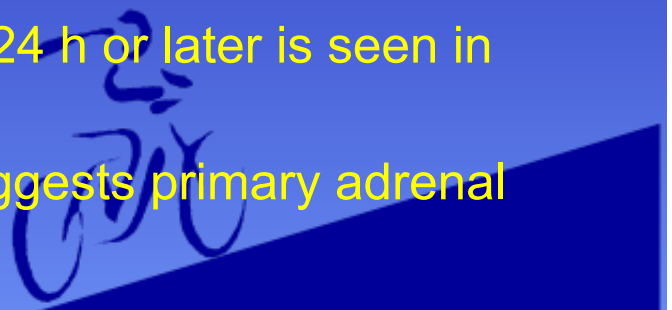


Figure 8.6 Algorithm for the investigation of hypoadrenalism.

Procedure & Interpretation

- Depot Synacthen 1 mg is given at 09.00 h by intramuscular injection. Blood samples are then taken at baseline, 1, 2, 4, 8 and 24 h for plasma cortisol concentration.
- Plasma cortisol values are usually between 600 nmol/L and 1600 nmol/L.
- The plasma cortisol concentrations should peak at 4–8 h.
- A delayed response peaking at 24 h or later is seen in secondary adrenal insufficiency.
- Plasma cortisol < 50 nmol/L suggests primary adrenal failure.



CORTICOSTEROID THERAPY

- There is a risk of adrenocortical hypofunction when long-term corticosteroid treatment is stopped suddenly.
- This may be due either to secondary adrenal atrophy or to impaired ACTH release.
- It is probably best to give the replacement hydrocortisone in three or more doses during the day.

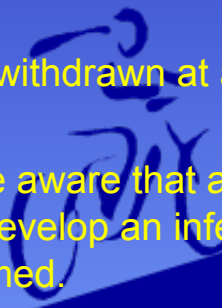
- Blood samples for cortisol can be collected during the day, aiming for a 09.00 h cortisol value of between 100 nmol/L and 700 nmol/L and in the afternoon ideally more than 100 nmol/L.
- Some patients require glucocorticoid therapy, for example for acute episodes of asthma or infl ammatory conditions such as rheumatoid arthritis, but then need their therapy withdrawn as their condition improves.

The main concern is that the hypothalamic–pituitary– adrenal axis has been suppressed, thereby putting the patient at risk of an adrenal crisis if treatment is stopped too quickly.

There are no universally agreed protocols to investigate this, but the following may be useful.

If therapy is short term, that is, less than 3 weeks, and the prednisolone dose equivalent is not higher than 40 mg, the steroid can be stopped with little likelihood of problems.

In cases where a higher dose of steroid equivalent has been used and for a longer time period, particularly if the steroid has been given in the evening or at night, gradual withdrawal IS important until 7.5 mg/day is reached.



Afterwards, the steroid dose should slowly be withdrawn at about 1 mg/day per month.

Patients should be observed closely and made aware that after withdrawal they are at a small risk of adrenal insufficiency if they develop an infection or undergo surgery, in which case steroid should be resumed.

If doubt persists once the steroids have been withdrawn, a short Synacthen test may reveal persistent adrenal insufficiency. Prednisolone 1 mg is approximately equivalent to 4 mg hydrocortisone and to 0.2 mg of dexamethasone.

CONGENITAL ADRENAL HYPERPLASIA

- The term congenital adrenal hyperplasia (CAH) embraces various defects involving enzymes of cortisol or aldosterone synthesis.
- Many of the enzymes involved in cortisol and aldosterone pathways are cytochrome p450. CYP21 refers to 21-α-hydroxylase, CYP11B1 refers to 11-b-hydroxylase and CYP17 to 17- α -hydroxylase.
- **All forms of CAH are rare.**
- An inherited deficiency (usually autosomal recessive) of one of the enzymes involved in the biosynthesis of cortisol, with a low plasma concentration, causes a high rate of secretion of ACTH from the anterior pituitary gland.
- This results in hyperplasia of the adrenal cortex, with increased synthesis of cortisol precursors before the enzyme block.
- The precursors may then be metabolized by alternative pathways, such as those of androgen synthesis. Increased androgen production may cause:

- *female pseudohermaphroditism*, by affecting the development of the female genitalia in utero; ambiguous genitalia may show phallic enlargement, clitoromegaly and early pubic hair,
- *virilization in childhood*, with phallic enlargement in either sex, development of pubic hair and a rapid growth rate,
- *milder virilization in females* at or after puberty, with amenorrhoea.

All female infants with ambiguous genitalia should have plasma electrolytes estimated and evidence of adrenocortical insufficiency looked for.

In male infants with no obvious physical abnormalities the diagnosis of CAH may not be suspected.

The most common form of CAH is CYP21 deficiency, which accounts for about 90 % of cases.

Females have ambiguous genitalia at birth (classic) or later in adolescence (non-classic with milder enzyme deficiency) and become virilized.

Males with CYP21 deficiency are not usually diagnosed in the neonatal period, as their genitalia are normal. However, if severe, the infant may present with salt wasting with vomiting, dehydration, failure to thrive and shock.

Aldosterone synthesis may be markedly reduced in more than half of the infants with 21- α -hydroxylase deficiency and may cause an Addisonian-like picture with marked renal sodium loss during the first few weeks of life.

Volume depletion may be accompanied by hyponatraemia and hyperkalaemia.

- Even if plasma sodium concentrations are within the reference range, demonstrably increased plasma renin activity may suggest lesser degrees of sodium and water depletion.
- CYP11B1 deficiency may also present with female ambiguous genitalia and salt loss.
- The child may, however, show hypertension and a hypokalaemic alkalosis.
- The enzyme CYP11B1 catalyses the conversion of 11-deoxycortisol to cortisol in the glucocorticoid pathway and the conversion of deoxycorticosterone to corticosterone in the mineralocorticoid pathway.
- CYP11B2 or aldosterone synthetase deficiency results in hyponatraemia and hyperkalaemia, although normal sexual differentiation occurs, as sex steroids are normal.
- In CYP17 deficiency, ambiguous genitalia or female genitalia may be observed in male infants. A female with CYP17 deficiency appears phenotypically female at birth but will fail to develop breasts or menstruate due to inadequate oestradiol production.
- Hypertension due to raised deoxycorticosterone concentration may be present in CYP17 deficiency

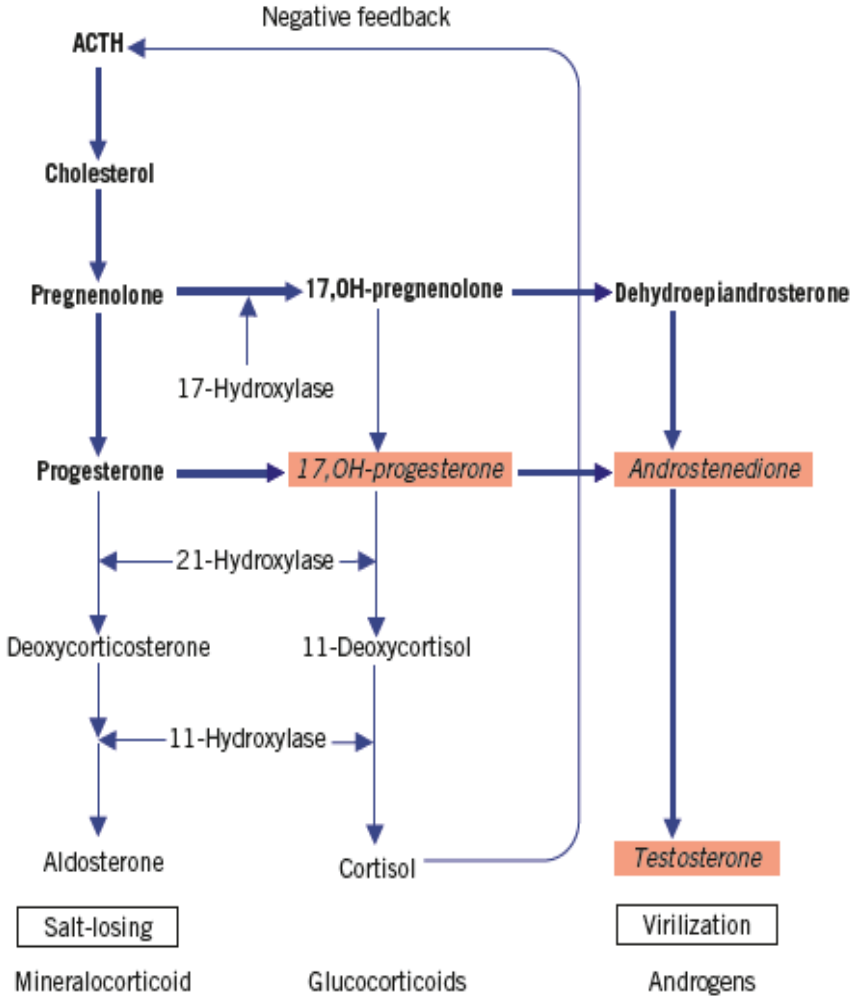


Figure 8.7 The abnormalities occurring in congenital adrenal hyperplasia. The substances highlighted are of diagnostic importance; those shown in bold are increased in 21-hydoxylase deficiency. ACTH, adrenocorticotrophic hormone.

Diagnosis

- 17-Hydroxyprogesterone can be metabolized by the cortisol pathway only in the presence of 21-α-hydroxylase, and plasma concentrations are raised in patients with CAH.
- Plasma androstenedione concentrations may be raised in those patients with excessive androgen synthesis.
- Some indication of which enzyme is deficient may be suggested by evaluating the pattern of steroid excretion in a random or 24-h urine sample.
- In 11-b-hydroxylase deficiency there is a raised concentration of 24-h urinary tetrahydrocortisol, a metabolite of 11-deoxycortisol, and raised deoxycorticosterone concentration.
- In the salt-losing forms, plasma renin and aldosterone concentrations may assist diagnosis.
- If a diagnosis of CAH is confirmed, genetic counselling may be necessary, with deoxyribonucleic acid (DNA) and family studies.

Treatment

- Congenital adrenal hyperplasia is treated by giving a glucocorticoid, for example hydrocortisone, and, if necessary, a mineralocorticoid, for example fludrocortisone.
- This treatment not only replaces the deficient hormones but, by negative feedback, also suppresses ACTH secretion and therefore androgen production.
- Measuring 17-hydroxyprogesterone and androstenedione concentrations in plasma or saliva enables treatment efficacy to be monitored.
- Salivary steroid concentrations correlate well with those in plasma, and saliva collection may be more acceptable to some patients than repeated venepuncture.
- . Measuring the plasma renin activity may help assess mineralocorticoid replacement.

PRIMARY HYPERALDOSTERONISM (CONN'S SYNDROME)

- Primary hyperaldosteronism (PH) is considered an important cause of secondary hypertension in perhaps as many as 5–15 % of cases, particularly in the face of hypokalaemia and kaliuria (e.g. urinary potassium more than 20 mmol/L).

- The majority of cases of PH are due to adrenal aldosterone-producing adenomas (APAs), which produce 18-oxocortisol and 18-hydroxycortisol steroids in excess, although 45 % of cases may be due to bilateral idiopathic adrenal hyperplasia (IAH).
- There is also a genetic–familial variety of PH.
- Type 1 familial PH is glucocorticoid remediable aldosteronism (GRA), in which the associated hypertension responds to small doses of glucocorticoids in addition to antihypertensives.
-

- The treatment of IAH is usually medical, and the mineralocorticoid antagonist spironolactone has proved useful, sometimes in conjunction with a thiazide diuretic.
- The treatment of choice for unilateral variants of PH such as APA is usually surgical by adrenalectomy

Investigation of a patient with suspecte primary hyperaldosteronism

Screening tests

- A urinary potassium is thus a useful screening test.
- In PH, plasma aldosterone concentration will be raised, with suppressed renin levels.

- A random plasma aldosterone to renin ratio of more than 750, where aldosterone is expressed in pmol/L and renin activity in μg/L per hour, is suggestive of PH and may be used as a screening test.
- This ratio is increased by b-blockers and decreased by angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium channel blockers and angiotensin II receptor blockers.
- A raised 24-h urinary aldosterone excretion may also be a useful screening tool.
- In summary ACE inhibitors&Ca channel blockers increase renin and reduce aldosterone, b-blockers reduce renin and aldosterone,
- and diuretics increase renin and aldosterone, although α-blocking drugs may have minimal effect upon renin and aldosterone concentrations.

- Treatment
- Adrenal adenomas producing aldosterone are usually surgically removed, sometimes by laparoscopic adrenalectomy.
- Hyperplasia of the adrenal glands can be treated with amiloride or spironolactone.
- Eplerenone is a selective aldosterone receptor antagonist, which may prove useful in preference to spironolactone. The glucocorticoid-remediable form of aldosteronism may respond to dexamethasone (Fig.

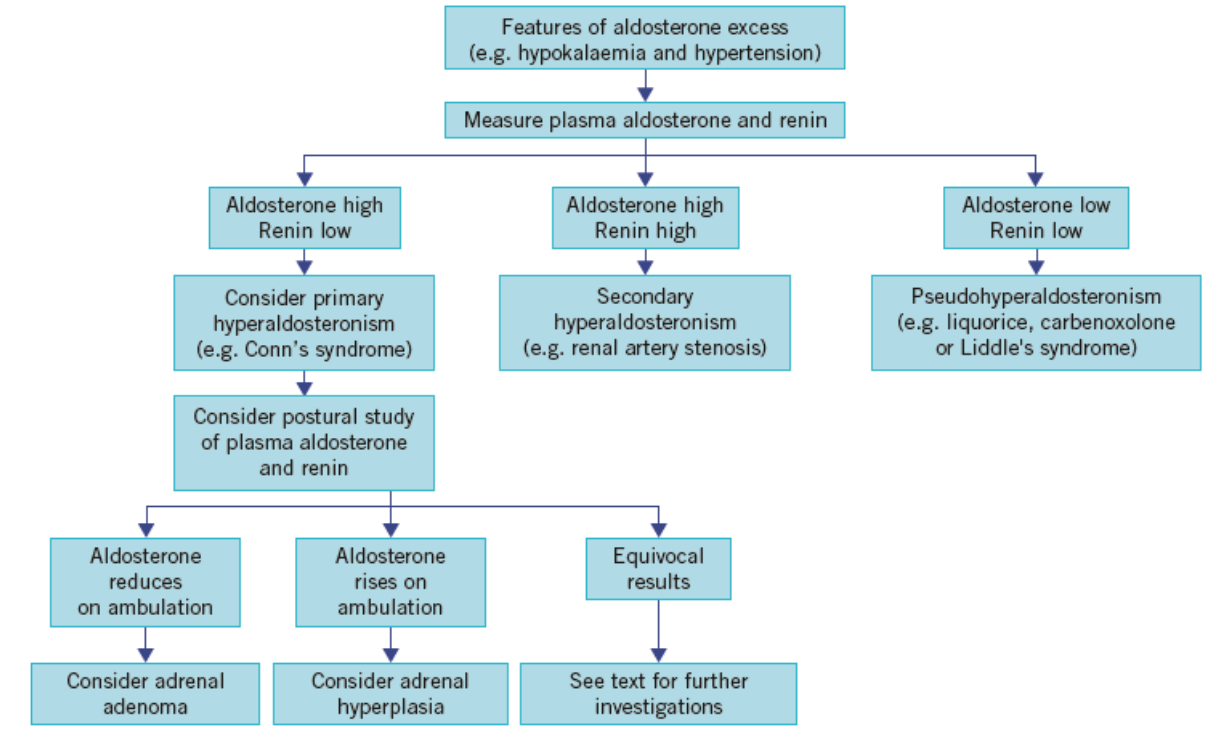


Figure 8.8 Algorithm for the investigation of hyperaldosteronism.