**ADRENOCORTICAL INSUFFICEINCY**

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Adrenal insufficiency is a condition in which there is destruction of the adrenal cortex and subsequent reduction in the output of adrenal hormones, ie glucocorticoids (cortisol) and/or mineralocorticoids (aldosterone).

* Primary insufficiency - there is an inability of the adrenal glands to produce enough steroid hormones.
* Secondary insufficiency - there is inadequate pituitary or hypothalamic stimulation of the adrenal glands

**Aetiology**

* Addison's disease is the term used to describe primary adrenal insufficiency but it can have many causes. In Western Europe, 85% of cases of Addison's disease now have an **autoimmune** basis. **Tuberculosis (TB)** was the most common cause in the first half of the 20th century and remains a common cause elsewhere in the world.
* Autoimmune adrenal destruction is isolated in **40% of cases**, and part of an autoimmune polyendocrinopathy syndrome **in 60%.** There is progressive destruction of the adrenal glands via immune mechanisms. Antibodies against steroid 21-hydroxylase can be found in about 85% of patients. Clinical and biochemical insufficiency only occurs once >90% of the gland is destroyed.
* **Administration of exogenous steroids is the most common cause of secondary insufficiency**

**Causes of adrenal insufficiency**

**Primary adrenal insufficiency**

**Anatomic destruction of the gland (acute or chronic)**:

* Addison's disease (autoimmune; 85% of cases).
* Surgical removal.
* Trauma.
* Infections - eg, tuberculosis (TB), histoplasmosis, cryptococcosis, HIV, syphilis.
* Haemorrhage - eg, anticoagulants, Waterhouse-Friderichsen syndrome.
* Infarction - eg, antiphospholipid syndrome.
* Invasion - eg, neoplastic, sarcoidosis, amyloidosis, haemachromatosis.

**Metabolic failure in hormone production**:

* Congenital adrenal hyperplasia - eg, 21-hydroxylase deficiency, 3-beta-hydroxysteroid dehydrogenase deficiency
* Enzyme inhibition - eg, ketoconazole, , etomidate and metapyrone.
* Accelerated hepatic metabolism of cortisol - eg, phenytoin, barbiturates, rifampicin.
* Adrenocorticotropic hormone (ACTH) or glucocorticoid resistance.
* Cytotoxic agents.

**Other causes**:

* ACTH-blocking antibodies.
* Mutation in ACTH receptor gene.
* Adrenal hypoplasia congenita.
* Familial adrenal insufficiency.
* Metabolic disorders - eg, Smith-Lemli-Opitz syndrome, Wolman's disease, adrenoleukodystrophy.
* Mitochondrial disorders - eg, Kearnes-Sayre syndrome.

**Secondary adrenal insufficiency**.

**Hypothalamic-related**:

* Congenital.
* Corticotropin-releasing hormone (CRH) deficiency.
* Trauma - eg, fracture of the skull base.
* Radiotherapy.
* Surgery.
* Neoplasm, primary or metastatic.
* Infiltration or infection - eg, sarcoidosis, haemachromatosis, lymphocytic hypophysitis, TB, meningitis.

**Suppression of hypothalamic-pituitary axis**:

* Exogenous steroid administration.
* Antipsychotic medication - eg, chlorpromazine.

**Pituitary**:

* Congenital - eg, aplasia.
* Tumours - eg, cysts, adenomas, meningiomas, craniopharyngiomas.
* Panhypopituitarism of any cause - eg, Sheehan's syndrome.
* Infection or infiltration - eg, TB, meningitis, sarcoidosis, haemachromatosis, lymphocytic hypophysitis.
* Radiotherapy.
* Trauma.
* Surgery.
* Isolated ACTH deficiency.

## Presentation

* **Acute**: presentation may be as a crisis precipitated by infection, surgery or trauma. In these situations, features include hypotension, hypovolaemic shock, acute abdominal pain, low-grade fever and vomiting. Sudden onset of insufficiency, such as the Waterhouse-Friderichsen syndrome (infarction secondary to septicaemia - eg, meningococcal) presents with collapse and shock.
* **Chronic** - symptoms develop insidiously and may be mild.

Persistent nonspecific symptoms which should provoke consideration of a diagnosis of adrenal insufficiency include:

* Fatigue and weakness (common feature).
* Anorexia.
* Nausea.
* Vomiting.
* Weight loss.
* Abdominal pain.
* Diarrhoea.
* Constipation.
* Cravings for salt and salty foods such as soy sauce or liquorice (primary insufficiency).
* Muscle cramps and joint pains.
* Syncope or dizziness (due to hypotension).
* Confusion.
* Personality change.
* Irritability.
* Loss of pubic or axillary hair in women, delayed puberty in children.

**Signs**

* Hyperpigmentation - look at buccal mucosa, lips, palmar creases, new scars and in areas subject to pressure such as elbows, knuckles and knees. (Not present in secondary adrenal insufficiency.)
* Hypotension.
* Postural hypotension.

Other situations which should provoke consideration of Addison's disease include:

* People with hypothyroidism in whom symptoms get worse when thyroxine treatment is commenced.
* Unexplained recurrent episodes of hypoglycaemia in people with type 1 diabetes. (Hypoglycaemia can be the presenting symptom in children.)
* Presence of other autoimmune diseases.
* Low sodium and high potassium levels. (Not necessarily present but common in established Addison's disease.)

### Laboratory abnormalities in adrenal insufficiency

 **Sodium** - reduced in 90% of newly diagnosed cases of primary adrenal insufficiency.

 **Potassium** - raised in 50% of newly diagnosed cases of primary adrenal insufficiency.

 **Calcium** - raised in 10-20 % of newly diagnosed cases of primary adrenal insufficiency.

 **FBC** - there may be anaemia, mild eosinophilia and lymphocytosis.

 **Glucose** - often low in children.

 **LFTs** - may be raised liver transaminases.

 **Cortisol** - usually reduced:

 **ACTH** (also known as corticotropin) - when measured together with cortisol allows differentiation of primary vs secondary insufficiency:

* Levels are raised in primary insufficiency.
* Levels are low or low normal in secondary insufficiency.

Plasma **renin and aldosterone levels** - will give an indication of mineralocorticoid activity. (Renin is often high and aldosterone low in Addison's disease. Usually unaffected in secondary insufficiency.)

### Other investigations

* An ACTH stimulation (Synacthen®) test may be required to confirm the diagnosis. ACTH is administered IV or IM, and cortisol levels subsequently measured. The normal response is a rise in cortisol level; in adrenal insufficiency this does not occur.
* An insulin tolerance test is occasionally used to confirm a diagnosis of secondary adrenal insufficiency - hypoglycaemia is induced by an insulin infusion and the cortisol response is monitored; this is not regularly performed due to safety issues.
* Investigations are required to establish the cause of the adrenal malfunction, as this will obviously influence management. This will depend on presentation, and whether it appears to be a primary or secondary insufficiency, but may include:
  + Adrenal autoantibodies - if negative, consider investigating for other causes (eg, TB).
  + CXR - to exclude lung neoplasm.
  + Abdominal X-ray - any adrenal calcification which may indicate previous TB infection.
  + CT scan of the adrenal glands if autoantibodies are negative.
  + MRI scan of hypothalamus and pituitary where central causes of adrenal insufficiency are suspected.
  + Tests of other hormones of the hypothalamic-pituitary axis - eg, TSH, prolactin, FSH/LH.
  + Screening for adrenoleukodystrophy (males only, X-linked condition) by measuring very long-chain fatty acids in a serum sample.

## Associated disease

At least 40-50% of those with Addison's disease will develop an associated endocrine abnormality

**Polyglandular autoimmune syndrome**

**Type 1**

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| **Main features**: | Triad of the following:   * Adrenal insufficiency. * Chronic hypoparathyroidism. * Chronic candidiasis. |
| **Other features:** | Include:   * Type 1 diabetes mellitus. * Pernicious anaemia. * Thyroid disorders. * Immunoglobulin A deficiency. * Chronic active hepatitis. * Alopecia. * Vitiligo. * Keratoconjunctivitis. * Chronic atopic dermatitis. * Hypogonadism. |

**Type 2**

**Main features**: Autoimmune adrenal insufficiency and:

* Autoimmune thyroid disease; and/or
* Type 1 diabetes mellitus.
* **Other features**: Premature ovarian deficiency.
* Vitiligo.
* Chronic atrophic gastritis and vitamin B12 deficiency.
* Coeliac disease.
* Hypoparathyroidism.

## Management

### Patient education

* Information about the condition.
* Medical emergency identification bracelet or similar.
* Steroid card.
* Importance of not missing steroids and not stopping them abruptly.
* Intercurrent illness - if tolerating oral medication then the dose should be doubled until better. If the patient is so unwell that they are unable to take the medication orally then they will need to take it parenterally - thus, they will need to be given IM hydrocortisone and be taught how to administer it.
* **Glucocorticoid replacement** - hydrocortisone is the mainstay of treatment; usually 15-30 mg in three divided doses with the highest dose in the morning (thus stimulating the normal diurnal adrenal rhythm). Twice daily regimens are also used, although opinion on their benefit varies. A modified-release once-daily preparation is also now available and licensed for use, and is still being evaluated.
* During minor illness or minor surgery, glucocorticoid doses may be increased up to three times their normal dose to avoid adrenal crisis, and up to ten times for major illness or major surgery.
* If there is co-existent thyroid deficiency then thyroid hormones should not be replaced before glucocorticoids, as a crisis may be precipitated.
* **Mineralocorticoid replacement** - this is usually required in primary adrenal insufficiency. Fludrocortisone is used and the usual adult dose is 50-300 micrograms per day, depending on activity levels, weight and metabolism.
* Assessing adequacy of therapy involves monitoring symptoms and signs, measuring blood pressure and looking for postural hypotension and normalising of serum electrolytes (Na and K).
  + Signs of over-replacement include raised blood pressure, thin skin, striae, easy bruising, glucose intolerance, hyperglycaemia and electrolyte abnormalities.
  + Signs of under-replacement are the symptoms of Addison's disease persisting, ie fatigue, postural hypotension, nausea, weight loss, and salt craving.

Because of the high incidence of other autoimmune disease, those with an autoimmune cause should be screened annually with:

* TFTs.
* Glucose and HbA1c.
* FBC.
* Vitamin B12.
* Coeliac screen if symptoms suggest.

### Management of adrenal crisis

Management involves admission to hospital, often to a critical care unit for intensive monitoring. The condition is managed with high-dose hydrocortisone parenterally and IV fluids.

People treated for adrenal insufficiency should be prescribed, and shown how to use, an emergency hydrocortisone self-injection kit, particularly for use when travelling or when medical care is not immediately available.

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