Addison's Disease: Primary Adrenocortical Insufficiency

Addison’s disease, also known as primary adrenal insufficiency or primary adrenocortical insufficiency, is a progressive and insidious disorder characterized by insufficient production of adrenal cortical hormones due to dysfunction or destruction of the adrenal cortex. It was first clinically described by Thomas Addison in 1855.

In Addison’s disease, the adrenal cortex fails to produce adequate amounts of glucocorticoids, mineralocorticoids, and androgens. This leads to elevated plasma adrenocorticotropic hormone (ACTH) levels due to the loss of negative feedback inhibition.

Causes

- **Autoimmune destruction** of the adrenal cortex (most common in developed countries)
- **Infectious causes** such as:
    - Tuberculosis (leading cause worldwide)
    - Fungal infections (e.g., histoplasmosis)
    - Cytomegalovirus infection (especially in immunocompromised patients)
- **Other causes**:
    - Metastatic carcinoma to adrenal glands
    - Amyloidosis
    - Hemochromatosis
    - Bilateral adrenal hemorrhage (e.g., anticoagulant therapy, trauma, childbirth)
    - AIDS-related opportunistic infections
    - Drugs inhibiting steroidogenesis (e.g., ketoconazole, etomidate)

Pathophysiology

Mineralocorticoid Deficiency

- Mineralocorticoids (primarily aldosterone) regulate sodium reabsorption and potassium excretion in kidneys.
- Deficiency causes:
    - Sodium loss ? hyponatremia
    - Potassium retention ? hyperkalemia
    - Loss of water ? dehydration, hypovolemia
    - Resultant symptoms: hypotension, plasma hypertonicity, metabolic acidosis, and circulatory collapse.
- Secondary adrenal insufficiency (due to pituitary failure) typically spares mineralocorticoid secretion; hence, electrolytes may remain normal or mildly altered.

Glucocorticoid Deficiency

- Glucocorticoids (cortisol) maintain glucose metabolism, stress response, and cardiovascular function.
- Deficiency results in:

    - Hypoglycemia due to impaired gluconeogenesis
    - Increased insulin sensitivity
    - Weakness and lethargy from neuromuscular dysfunction
    - Reduced resistance to infection and trauma
    - Myocardial weakness and decreased cardiac output
- Elevated ACTH and ?-lipotropin stimulate melanocytes causing **hyperpigmentation** of skin and mucous membranes—a hallmark of primary adrenal insufficiency (absent in secondary insufficiency).

Clinical Manifestations

General Features

- Gradual onset of fatigue, weakness, and weight loss
- Dehydration and hypotension (often orthostatic)
- Salt craving due to hyponatremia

Due to Mineralocorticoid Deficiency

- Hyponatremia, hyperkalemia
- Hypotension, dehydration
- Cardiovascular collapse in severe cases

Due to Glucocorticoid Deficiency

- Poor stress tolerance
- Hypoglycemia (causing weakness, lethargy, and confusion)
- Gastrointestinal symptoms: anorexia, nausea, vomiting, abdominal pain
- Hyperpigmentation: bronze or suntanned appearance, especially in sun-exposed and pressure areas; mucosal pigmentation including gums and oral mucosa
- Sparse axillary and pubic hair in women
- Cold intolerance and hypometabolism

Adrenal Crisis (Acute Adrenal Insufficiency)

- Severe asthenia and abdominal, back, or leg pain
- Peripheral vascular collapse and shock
- Renal failure with azotemia
- Hypothermia or fever (especially if precipitated by infection)
- May present with only shock and fever

Diagnosis

- Clinical suspicion based on symptoms and signs
- Laboratory tests:
    - Serum electrolytes: hyponatremia, hyperkalemia
    - Low serum cortisol (< 5 ?g/dL or < 138 nmol/L)
    - Elevated plasma ACTH (? 50 pg/mL)
- ACTH stimulation test to confirm diagnosis

- Other investigations to identify underlying cause (e.g., imaging, autoimmune markers)

Treatment

Chronic Management

- Lifelong hormone replacement therapy with glucocorticoids and mineralocorticoids
- **Glucocorticoid replacement**:
  - Hydrocortisone (identical to cortisol) is preferred: 15–30 mg/day divided into 2 or 3 doses (e.g., 10 mg morning, 5 mg midday, 5 mg late afternoon)
- **Mineralocorticoid replacement**:
  - Fludrocortisone 0.1–0.2 mg daily PO for aldosterone replacement in primary adrenal insufficiency
- Dehydroepiandrosterone (DHEAS) supplementation may benefit some female patients
- Stress dose adjustments during illness, surgery, or trauma are essential
- Patients should maintain regular meals and exercise to prevent hypoglycemia

Adrenal Crisis Management

- Immediate intravenous hydrocortisone 100 mg bolus over 30 seconds, repeated every 6–8 hours
- Rapid volume resuscitation with isotonic saline and 5% dextrose to correct hypotension, dehydration, and electrolyte imbalances
- Monitor and maintain blood pressure and serum electrolytes closely
- Gradual tapering to maintenance doses over subsequent days
- Hospitalization and supportive care are mandatory

Patient Education and Precautions

- Patients should wear medical alert identification indicating adrenal insufficiency
- Education on stress dose adjustments and emergency management
- Immediate medical attention is critical during infections, trauma, or surgery