ADRENAL DISORDERS - 2

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HYPOADRENALISM

- Primary hypoadrenalism: glucocorticoid deficiency due to adrenal disease
- Secondary hypoadrenalism: ACTH deficiency due to pituitary disease
- (Tertiary hypoadrenalism: hypothalamic disease)

Major difference: mineralocorticoid deficiency invariably accompanies primary hypoadrenalism but does not occur in secondary hypoadrenalism because only ACTH is deficient; the renin-angiotensin-aldosterone axis is intact

Etiology of adrenocortical insufficiency

PRIMARY: ADDISON’S DISEASE

- Autoimmune (Sporadic, Autoimmune polyendocrine syndrome type I and type II)
- Infections (Tuberculosis, Fungal infections, Cytomegalovirus, HIV)
- Metastatic tumor
- Infiltrations (Amyloid, Hemochromatosis)
- Intra-adrenal haemorrhage (Waterhouse-Friderichsen syndrome) after meningococcal septicaemia
- Adrenoleukodystrophies
- Congenital adrenal hypoplasia
- ACTH resistance syndromes
- Bilateral adrenalectomy

SECONDARY

- Exogenous glucocorticoid therapy
- Hypopituitarism
- Selective removal of ACTH-secreting pituitary adenoma
- Pituitary tumors and pituitary surgeons; craniopharyngiomas
- Pituitary apoplexy
- Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
- Secondary tumor deposits (breast, bronchus)
- Postpartum pituitary infarction (Sheehan’s syndrome)
- Pituitary irradiation (effect usually delayed for several years)
- Isolated ACTH deficiency
- Lymphocytic hypophysitis
- POMC (pro-opiomelanocortin) processing defect, POMC gene mutations
- Idiopathic

Primary Hypoadrenalism

Addison’s Disease

- Thomas Addison described this condition in his classical monograph published in 1855.
- Rare condition, incidence of 0.8 cases per 100,000 and prevalence of 4 to 11 cases per 100,000 population

Autoimmune Adrenalitis

- Autoimmune adrenalitis accounts for > 70% of cases
- The adrenal glands are atrophic, with loss of most of the cortical cells, but the medulla is usually intact
- In 75% of cases adrenal autoantibodies can be detected
- 50% of patients have an associated autoimmune disease, thyroid disease being the commonest
- These autoimmune polyendocrine syndromes (APS I and II) have been classified into two distinct variants
- APS type I
  - Addison’s disease, chronic mucocutaneous candidiasis, hypothyroidism, dental enamel hypoplasia, alopecia, primary hypogonadism
- APS type II (Schmidt’s syndrome)
  - Addison’s disease, primary hypothyroidism, primary hypogonadism, insulin-dependent diabetes, pernicious anaemia, dilated cardiomyopathy
Incidence of other endocrine and autoimmune diseases in patients with autoimmune adrenal insufficiency

- **Thyroid disease**
  1. Hypothyroidism 8%
  2. Nontoxic goiter 7%
  3. Thyrotoxicosis 7%

- **Gonadal failure**
  1. Ovarian 20%
  2. Testicular 2%
  3. Insulin-dependent diabetes mellitus 11%
  4. Hypoparathyroidism 10%
  5. Pernicious anemia 5%
  6. None 53%

Clinical manifestations of APS (prevalence)

**APS type I**

- **Endocrine**
  1. Hypothyroidism 69%
  2. Chronic mucocutaneous candidiasis 75%
  3. Adrenal insufficiency 60%
  4. Gonadal failure 40%
  5. Hypoparathyroidism 12%
  6. Insulin-dependent diabetes mellitus 1%
  7. Hypopituitarism <1%
  8. Diabetes insipidus <1%
- **Nonendocrine**
  1. Malabsorption syndromes 25%
  2. Alopecia totalis or areata 20%
  3. Pernicious anemia 16%
  4. Chronic active hepatitis 9%
  5. Vitiligo 4%

**APS type II**

- **Endocrine**
  1. Adrenal insufficiency 100%
  2. Autoimmune thyroid disease 70%
  3. Insulin-dependent diabetes mellitus 50%
  4. Gonadal failure 55%
  5. Diabetes insipidus <1%
- **Nonendocrine**
  1. Vitiligo 4%
  2. Alopecia, pernicious anemia, myasthenia gravis, ITP, Sjögren's syndrome, rheumatoid arthritis <1%

Presentation of the disease

- **Rate of onset and severity of adrenal deficiency**
- **In most cases:** insidious onset, diagnosis is made only when the patient presents with an acute crisis during an intercurrent illness
- **Acute adrenal insufficiency or an adrenal or addisonian crisis is a medical emergency manifesting as hypotension and acute circulatory failure**
- **Anorexia, progressing to nausea, vomiting, diarrhea, and sometimes abdominal pain, fever and hypoglycemia may be present**

Clinical Features of Adrenal Insufficiency

**Primary disease**
- Mineralocorticoid + glucocorticoid deficiency
- Skin pigmentation
- In the autoimmune form there might be vitiligo

**Secondary disease**
- Only glucocorticoid deficiency (RAAS intact)
- No skin pigmentation
- In the hypopituitary form there may be other hormone deficiency (LH, FSH, TSH)
Clinical features of Addison's disease

Symptoms (prevalence, %)
- Weakness, tiredness, fatigue: 100%
- Anorexia: 100%
- Gastrointestinal symptoms: 92%
  1. Nausea: 86%
  2. Vomiting: 75%
  3. Constipation: 33%
  4. Abdominal pain: 31%
  5. Diarrhea: 16%
- Salt craving: 16%
- Postural dizziness: 12%
- Muscle or joint pains: 13%

Signs and laboratory findings, prevalence (%)
- Weight loss: 100%
- Hyperpigmentation: 94%
- Hypotension (<110 mm Hg systolic): 88-94%
- Vitiligo: 10-20%
- Auricular calcification: 5%
- Electrolyte disturbances: 92%
  1. Hypernatremia: 88%
  2. Hyperkalemia: 64%
  3. Hypercalcemia: 6%
- Azotemia: 55%
- Anemia: 40%
- Eosinophilia: 17%

Clinical and laboratory features of an adrenal crisis
- Dehydration, hypotension, or shock out of proportion to severity of current illness
- Nausea and vomiting with a history of weight loss and anorexia
- Acute Abdominal pain
- Unexplained hypoglycemia
- Unexplained fever
- Hyperpigmentation, hyperkalemia, azotemia, hypercalcemia, or vitiligo
- Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal failure

Investigations
Routine biochemical investigations
- Hyponatremia (might be depletional or dilutional)
- Hyperkalaemia (due to aldosterone def., not present in secondary disease)
- Hypercalcemia
- TSH might be elevated, due to glucocorticoid def.

Assessing the Function of the Hypothalamo-Pituitary-Adrenal Axis
- Basal plasma cortisol and urinary free cortisol levels are often in the low normal range and cannot be used to exclude the diagnosis
- However, a basal cortisol value greater than 400 nmol/L (15 µg/dL) invariably indicates an intact HPA axis

Short tetracosactide (synacthen) test
Indication
- Diagnosis of Addison's disease
- Screening test for ACTH deficiency
Procedure
- Intravenous cannula for sampling
- Any time of day, but best at 0800 h; non-fasting
- Tetracosactide 250 µg (synthetic ACTH), i.v. or i.m. at time 0
- Measure serum cortisol at time 0 and time +30 min
Normal response
- 30 min cortisol > 600 nmol/L* (400-600 nmol/L borderline and may indicate deficiency
Short ACTH stimulation test
(Synacthen)
- response is unaffected by the time of day of the test
- the test can be performed in patients who have commenced corticosteroid replacement therapy provided this is of short duration and does not include hydrocortisone (which would cross-react in the cortisol assay)

Prolonged ACTH stimulation test
- depot or iv. infusions of tetraacosactrin for 24 to 48 hours
- differentiates primary from secondary hypoadrenalism
- in normal subjects: plasma cortisol at 4 hours is greater than 1000 nmol/L, and beyond this time there is no further increase
- in secondary hypoadrenalism: delayed response with usually a much higher value at 24 and 48 hours than at 4 hours
- in primary hypoadrenalism: there is no response at either time
- the test is now rarely required if plasma ACTH has been appropriately measured at baseline

Insulin tolerance test
- the insulin-induced hypoglycemia test was introduced over 30 years ago, for assessing the integrity of the HPA axis, and still should be considered the "gold standard"
- iv. administration of soluble insulin in a dose of 0.1 to 0.15 U/kg body weight with measurement of plasma cortisol at 0, 30, 45, 60, 90, and 120 minutes
- adequate hypoglycemia (blood glucose less than 39 µg/dL) with signs of neuroglycopenia, sweating and tachycardia is essential
- should not be performed in patients with ischemic heart disease (always check ECG before the test), epilepsy, or severe hypopituitarism (that is, 9 AM plasma cortisol less than 180 nmol/L)
- in normal subjects the peak plasma cortisol exceeds 500 nmol/L

Overnight metyrapone test and CRH stimulation test
- They are reserved for difficult diagnostic cases
- overnight metyrapone test: metyrapone is given at 30 mg/kg (maximum 3 g) at midnight and plasma cortisol is measured at 8 AM the following morning
- in patients with an intact axis, ACTH levels rise after the blockade of cortisol synthesis by metyrapone
- CRH stimulation test: it is used to diagnose adrenal insufficiency, and also differentiates primary from secondary causes
- in primary adrenal failure: high ACTH levels that rise further after CRH
- in secondary adrenal failure: low ACTH levels that fail to respond to CRH
- in hypothalamic disease: steady rise in ACTH levels after CRH

Other Tests
- Radioimmunoassay to detect autoantibodies such as those against the 21-hydroxylase antigen
- evidences of other organ-specific autoimmune diseases
- CT scan: enlarged or calcified adrenals, suggesting an infective, hemorrheic, or malignant diagnosis
- Chest radiograph, tuberculin testing, and early morning urine samples cultured for Mycobacterium tuberculosis should be obtained if tuberculosis is suspected
- CT-guided adrenal biopsy for suspected malignancy
- measuring the circulating levels of very-long-chain fatty acids for adrenoleukodystrophy
- pituitary MRI scans for secondary hypoadrenalism

Treatment of Acute Adrenal Insufficiency
- Acute adrenal insufficiency is a life-threatening emergency, and treatment should not be delayed while waiting for definitive proof of diagnosis
- Besides samples for plasma electrolytes and blood glucose, appropriate samples for ACTH and cortisol should be taken before giving corticosteroid therapy
- if the patient is not critically ill, an acute ACTH stimulation test can be performed
- Iv. hydrocortisone 100 mg every 6 hours (If iv. not possible, im. also can be used)
In the shocked patient: 1 L NS iv. over the first hour, and because of possible hypoglycemia, give 5% dextrose also.

Clinical improvement, especially in the blood pressure, should be seen within 4 to 6 hours if the diagnosis is correct.

Recognize and treat any associated condition, such as an infection, which may have precipitated the acute adrenal crisis.

After the first 24 hours the dose of hydrocortisone can be reduced:
- IM. hydrocortisone 50 mg 6 hourly
- Then to oral hydrocortisone, 40 mg in the morning and 20 mg at 6 PM
- This can then be rapidly reduced to a more standard replacement dose of 20 mg on wakening and 10 mg at 6 PM.

Treatment of adrenal crisis

Emergency Measures

1. Establish intravenous access with a large-gauge needle.
2. Draw blood for stat serum electrolytes and glucose and routine measurement of plasma cortisol and ACTH. Do not wait for laboratory results.
3. Infuse 2 to 3 L of 0.9% saline or 5% DNS solution as quickly as possible. Monitor for signs of fluid overload by measuring central or peripheral venous pressure and listening for pulmonary rales. Reduce infusion rate if indicated.
4. Inject intravenous hydrocortisone (100 mg immediately and every 6 hr)
5. Use supportive measures as needed.

Subacute Measures After Stabilization of the Patient

1. Continue iv. 0.9% saline at a slower rate for next 24 to 48 hr.
2. Search for and treat possible infectious precipitating causes of the adrenal crisis.
3. Perform a short ACTH stimulation test to confirm the diagnosis of adrenal insufficiency, if patient does not have known adrenal insufficiency.
4. Determine the type of adrenal insufficiency and its cause if it is not already known.
5. Taper glucocorticoids to maintenance dosage over 3 to 5 days, if precipitating or complicating illness permits.
6. Begin mineralocorticoid replacement therapy with fludrocortisone (0.1 mg by mouth daily) when saline infusion is stopped.

Chronic Replacement Therapy

The aim is to mimic the normal cortisol secretion rate
- Initially, this was thought to be approx. 25 to 30 mg/day, but stable isotope studies indicate lower normal cortisol production rates of 8 to 15 mg/day.
- Most patients can cope with less than 30 mg/day (usually 15 to 25 mg/day in divided doses).
- Doses are usually given on wakening, with a smaller dose in the late afternoon, but some patients may feel better with dosing three times daily.
- Decisions about doses of replacement therapy are largely based on end points such as weight, well-being, and blood pressure.
- Bone mineral density may be reduced with conventional hydrocortisone doses of 30 mg/day, highlighting the need to strive for minimally effective but safe doses.

Precautions for patients on replacement therapy

- In primary adrenal failure, mineralocorticoid replacement is also required in the form of fludrocortisone at 0.05 to 0.2 mg/day.
- The adequacy of mineralocorticoid replacement should be assessed by measuring:
  - Electrolytes
  - Supine and erect blood pressure
  - Plasma renin activity
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Treatment of chronic Addison

Summary

Glucocorticoid Replacement
- Hydrocortisone 15-20 mg on awakening and 5-10 mg in early afternoon.
- Monitor clinical symptoms and morning plasma ACTH.

Mineralocorticoid Replacement
- Fludrocortisone 0.1 (0.05-0.2) mg orally.
- Liberal salt intake.
- Monitor lying and standing blood pressure and pulse, edema, serum potassium, and plasma renin activity.

→ Educate patient about the disease, how to manage minor illnesses and major stresses, and how to inject steroid intramuscularly.
→ Obtain Medic Alert bracelet/necklace, Emergency Medical Information Card.