CASE FIVE

Short case number: 3_17_5
Category: Endocrine & Reproductive Systems.
Discipline: Medicine
Setting: Emergency Department
Topic: Adrenocortical Insufficiency.

Case

John Mosby, 25 years old, has a long history of chronic asthma, which has required long term use of inhaled and oral corticosteroids to manage.

He has been unwell over the last few days with vomiting and diarrhoea and presents with lethargy and looks pale and unwell.

Questions

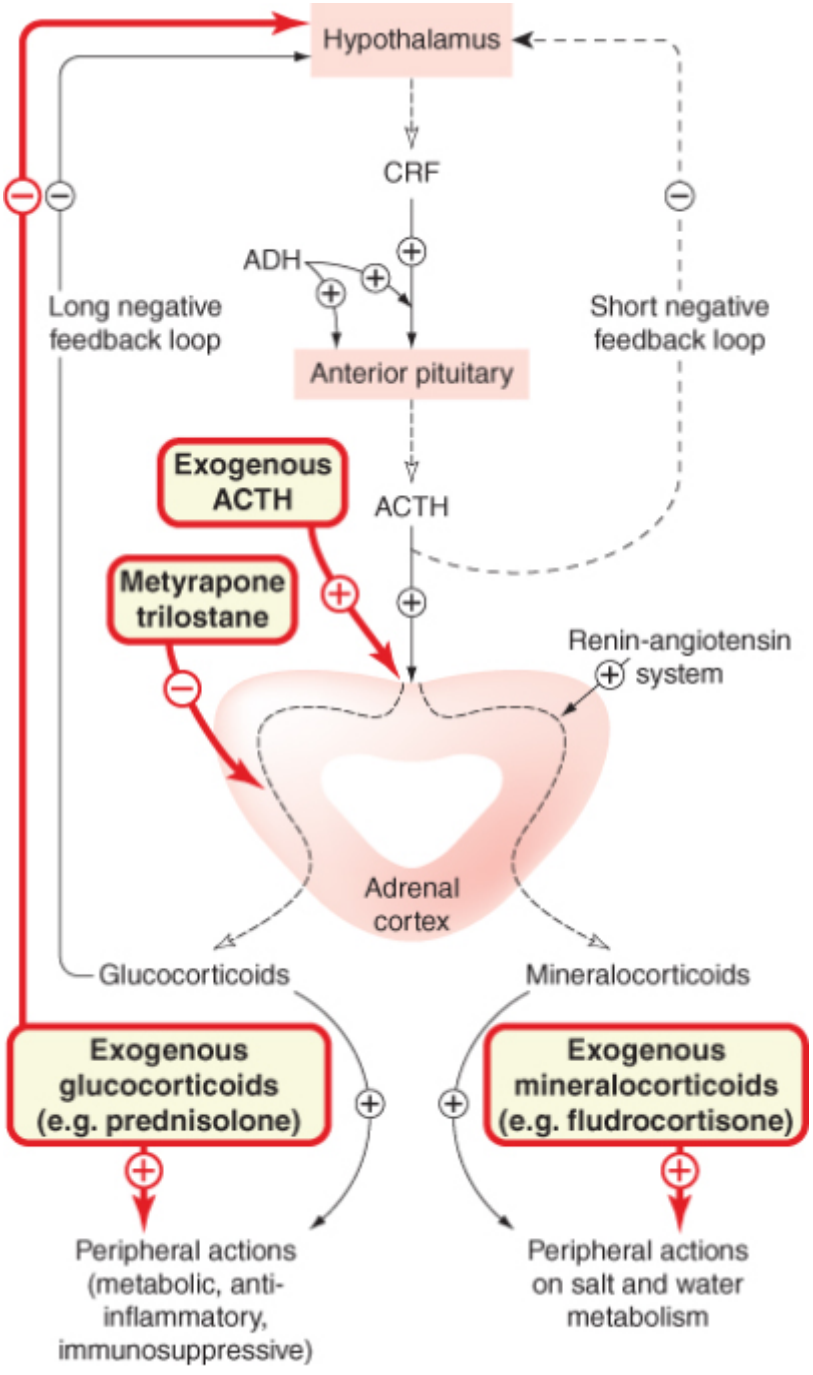
1. The ED registrar explains to you that his long term use of steroid medication has most likely impaired John's ability to respond to his illness; demonstrate your understanding of the glucocorticoid axis by explaining what the registrar means by this.
2. Outline other potential problems due to prolonged use of corticosteroid medications.
3. Long-term steroid use is the most common cause of secondary adrenocortical insufficiency. Outline in a table other causes of adrenal insufficiency and summarise how secondary and primary adrenocortical insufficiency differ.
4. What are the key clinical and biochemical features of adrenal insufficiency?
5. Why is primary hypoadrenalism [Addison disease] potentially life threatening?
6. Summarise the key investigations in the patient with suspected adrenocortical insufficiency and correlate the results with the clinical context.
7. Summarise the principles of management of primary hypoadrenalism.

Suggested reading:

- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 9th edition. Edinburgh: Saunders Elsevier; 2016.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.
- Rang et al. Rang & Dale's Pharmacology, 6th Ed. Elsevier Saunders. 2007.

ANSWERS

1. The ED registrar explains to you that his long term use of steroid medication has most likely impaired John's ability to respond to his illness; demonstrate your understanding of the glucocorticoid axis by explaining what the registrar means by this.



Regulation of synthesis and secretion of adrenal corticosteroids. The long negative feedback loop is more important than the short loop (dashed lines). Adrenocorticotrophic hormone (ACTH, corticotrophin) has only a minimal effect on mineralocorticoid production. Drugs are shown in yellow boxes. ADH, antidiuretic hormone (vasopressin); CRF, corticotrophin-releasing factor.

2. Outline other potential problems due to prolonged use of corticosteroid medications.

Unwanted effects are seen mainly after prolonged systemic use as anti-inflammatory or immunosuppressive agents but not usually with replacement therapy. The most important are:

- suppression of response to infection
- suppression of endogenous glucocorticoid synthesis
- metabolic actions (see above)
- osteoporosis
- iatrogenic Cushing's syndrome

3. Long-term steroid use is the most common cause of secondary adrenocortical insufficiency. Outline in a table other causes of adrenal insufficiency and summarise how secondary and primary adrenocortical insufficiency differ.

CAUSES OF ADRENOCORTICAL INSUFFICIENCY

SECONDARY (↓ACTH) → Issue @ level of Anterior Pituitary (or Hypothalamus)
(1) Withdrawal of suppressive glucocorticoid therapy → Chronic supression of ACTH from steroid use leads to adrenal atrophy over time. → Sudden stop! = not enough cortisol
(2) Hypothalamic or pituitary disease
PRIMARY (↑ACTH) → Issue @ level of adrenal glands
Addison's disease Common Causes • Autoimmune (Sporadic, Polyglandular syndromes) • Tuberculosis • HIV/AIDS • Metastatic carcinoma • Bilateral adrenalectomy Rare causes • Lymphoma • Intra-adrenal haemorrhage (following meningococcal septicaemia) • Amyloidosis • Haemochromatosis **Corticosteroid biosynthetic enzyme defects** • Congenital adrenal hyperplasias • Drugs • Aminoglutethimide, metyrapone, ketoconazole, etomidate etc.

4. What are the key clinical and biochemical features of adrenal insufficiency?

	Glucocorticoid insufficiency	Mineralocorticoid insufficiency	ACTH excess	Adrenal androgen insufficiency
Withdrawal of exogenous glucocorticoid	+	-	-	+
Hypopituitarism	+	-	-	+
Addison's disease	+	+	+	+
Congenital adrenal hyperplasia (21 OHase deficiency)	+	+	+	-
Clinical features	Weight loss Malaise Weakness Anorexia Nausea Vomiting Gastrointestinal-diarrhoea or constipation Postural hypotension Shock Hypoglycaemia Hyponatraemia (dilutional) Hypercalcaemia	Hypotension Shock Hyponatraemia (depletional) Hyperkalaemia	Pigmentation Sun-exposed areas Pressure areas, e.g. elbows, knees Palmar creases, knuckles Mucous membranes Conjunctivae Recent scars	Decreased body hair and loss of libido, especially in female

5. Why is primary hypoadrenalism [Addison disease] potentially life threatening?

Features of an acute adrenal crisis include circulatory shock with severe hypotension, hyponatraemia, hyperkalaemia and, in some instances, hypoglycaemia and hypercalcaemia. Muscle cramps, nausea, vomiting, diarrhoea and unexplained fever may be present. The crisis is often precipitated by intercurrent disease, surgery or infection.

6. Summarise the key investigations in the patient with suspected adrenocortical insufficiency and correlate the results with the clinical context.

Investigations

In patients presenting with chronic illness, the investigations below should be performed before any treatment. In patients with suspected acute adrenal crisis treatment should not be delayed pending results. A random blood sample should be stored for measurement of cortisol.

Assessment of glucocorticoids

Random plasma cortisol is usually low in patients with adrenal insufficiency, but it may be within the normal range yet inappropriately low for a seriously ill patient. Random

measurement of plasma cortisol cannot therefore be used to confirm or refute the diagnosis, unless the value is high, i.e. > 460 nmol/l (> 170 µg/dl).

More useful is the short ACTH stimulation test (also called the tetracosactide or short Synacthen test). Cortisol levels fail to increase in response to exogenous ACTH in patients with primary or secondary adrenal insufficiency. These can be distinguished by measurement of ACTH (which is low in ACTH deficiency and high in Addison's disease). If an ACTH assay is unavailable, then a long ACTH stimulation test can be used (1 mg depot ACTH i.m. daily for 3 days); in secondary adrenal insufficiency there is a progressive increase in plasma cortisol with repeated ACTH administration, whereas in Addison's disease cortisol remains less than 700 nmol/l (25.4 µg/dl) at 8 hours after the last injection.

In a patient who is already receiving glucocorticoids, the short ACTH stimulation test can be performed first thing in the morning, > 12 hours after the last dose of glucocorticoid, or the treatment can be changed to a synthetic steroid such as dexamethasone (0.75 mg daily), which does not cross-react in the plasma cortisol immunoassay.

Assessment of mineralocorticoids
Plasma electrolyte measurements are insufficient to assess mineralocorticoid secretion in patients with suspected Addison's disease. Hyponatraemia occurs in both aldosterone and cortisol deficiency. Hyperkalaemia is common, but not universal, in aldosterone deficiency. Plasma renin activity and aldosterone should be measured in the supine position. In mineralocorticoid deficiency, plasma renin activity is high, with plasma aldosterone being either low or in the lower part of the normal range.

Other tests to establish the cause
In patients with elevated ACTH, further tests are required to establish the cause of Addison's disease. In those who have autoimmune adrenal failure, antibodies can often be measured against steroid-secreting cells (adrenal and gonad), thyroid antigens, pancreatic β cells and parietal cells. Thyroid function tests, full blood count (to screen for pernicious anaemia), plasma calcium, glucose and tests of gonadal function should be performed.
Other causes of adrenocortical disease are usually obvious clinically, particularly if health is not fully restored by corticosteroid replacement therapy. Tuberculosis causes adrenal calcification, visible on plain X-ray or ultrasound scan. A chest X-ray and early morning urine for culture should also be taken. An HIV test may be appropriate if risk factors for infection are present. Imaging of the adrenals by CT or MRI to identify metastatic malignancy may also be appropriate.

7. Summarise the principles of management of primary hypoadrenalism.

Management

Patients with adrenocortical insufficiency always need glucocorticoid replacement therapy and usually, but not always, mineralocorticoid. Adrenal androgen replacement for women is not usually employed. Other treatments depend on the underlying cause.

Glucocorticoid replacement

Cortisol (hydrocortisone) is the drug of choice. In someone who is not critically ill, cortisol should be given by mouth. The dose may need to be adjusted for the individual patient, but this is subjective. Excess weight gain usually indicates over-replacement, whilst persistent lethargy or hyperpigmentation may be due to an inadequate dose. Measurement of plasma cortisol levels is unhelpful, because the dynamic interaction between cortisol and glucocorticoid receptors is not predicted by measurements such as the maximum or minimum plasma cortisol level after each dose. These are physiological replacement doses which should not cause Cushingoid side-effects.

An adrenal crisis is a medical emergency and requires intravenous hydrocortisone succinate and intravenous fluid. Parenteral hydrocortisone should be continued until gastrointestinal symptoms abate before starting oral therapy. The precipitating cause should be sought and, if possible, treated.

Mineralocorticoid replacement

Aldosterone is not readily available and fludrocortisone (i.e. 9α-fluoro-hydrocortisone) is the mineralocorticoid used. The halogen group prevents fludrocortisone from being metabolised by 11β-HSD2 and thereby confers a longer half-life and access to mineralocorticoid receptors. Adequacy of replacement can be assessed objectively by measurement of blood pressure, plasma electrolytes and plasma renin activity.

In adrenal crisis, however, rapid replacement of sodium deficiency is more important than administration of fludrocortisone. Intravenous saline should be infused as required to normalise haemodynamic indices.

ADVICE TO PATIENTS ON GLUCOCORTICOID REPLACEMENT

Intercurrent stress: e.g. Febrile illness-double dose of hydrocortisone
Surgery: Minor operation-hydrocortisone 100 mg i.m. with pre-medication. Major operation-hydrocortisone 100 mg 6-hourly for 24 hours, then 50 mg i.m. 6-hourly until ready to take tablets
Vomiting: Must have parenteral hydrocortisone if unable to take by mouth
Steroid card: Patient should carry this at all times. Should give information regarding diagnosis, steroid, dose and doctor
Bracelet: Patients should be encouraged to buy one of these and have it engraved with the diagnosis and a reference number for a central database