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Citation for final published version:

Rees, Dafydd Aled 2018. Tips from the shop floor: Addisonian crisis - assessment and management. *British Journal of Hospital Medicine* 79 (3) , pp. 34-37. 10.12968/hmed.2018.79.3.C34

Publishers page: <http://dx.doi.org/10.12968/hmed.2018.79.3.C34>

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‘Tips from the shop floor: Addisonian crisis – assessment and management’

Introduction

An ‘Addisonian crisis’ is one of the most feared endocrine emergencies and requires early recognition and prompt treatment to prevent serious consequences. Strictly-speaking, Addison’s disease describes an autoimmune adrenalitis leading to cortisol deficiency. However, the term ‘Addisonian crisis’ is often used on the acute medical take to describe the acute clinical presentation associated with adrenal failure, irrespective of the underlying aetiology. Cortisol deficiency originating from the adrenal gland is known as primary adrenal insufficiency (PAI) whereas if the origin is from the pituitary or hypothalamus then this is known as secondary adrenal insufficiency. (Figure 1).

This article aims to summarise the causes of adrenal insufficiency in a manner that is easy to remember and to revise the symptoms and signs of its acute presentation. The emergency medical management will be presented together with top tips for treating and investigating the condition up until discharge.

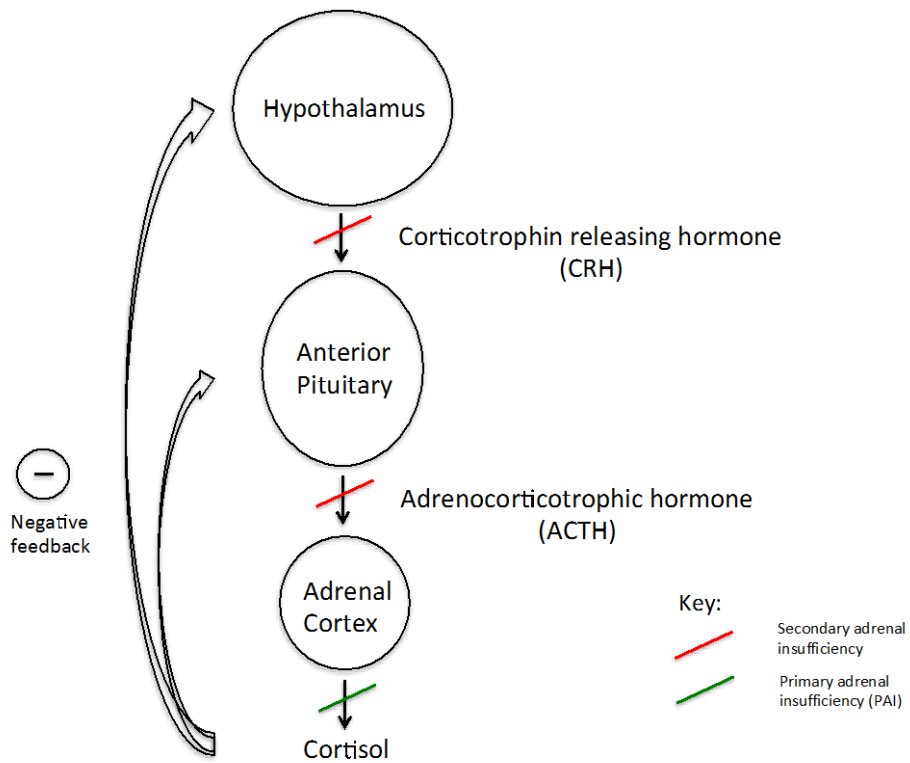
Aetiology

Primary and secondary causes of adrenal insufficiency can be broadly divided into causes using the “I” mnemonic: **I**mmunological, **I**nvasion, **I**nfection, **I**nfiltration, **I**atrogenic, **I**nfants (congenital) and **I**njury (Table 1).

Table 1: Causes of primary and secondary adrenal insufficiency using the “I” mnemonic

Causes	Primary	Secondary
“Immunological”	Isolated autoimmune adrenalitis (Addison’s Disease), autoimmune polyglandular syndromes	Lymphocytic hypophysitis
“Invasion”	Bilateral adrenal metastasis, lymphoma	Pituitary tumours (e.g. Macroadenoma, craniopharyngioma, meningioma, metastasis)
“Infection”	Tuberculosis, HIV, CMV, fungal infections	Tuberculosis, histoplasmosis
“Infiltration”	Sarcoidosis, amyloidosis, hemochromatosis,	Granulomatosis with polyangiitis (Wegener’s granulomatosis), Sarcoidosis, amyloidosis, hemochromatosis,
“Infarction”	Haemorrhage, Waterhouse-Friderichsen syndrome, antiphospholipid syndrome, hypoperfusion, anti-coagulant therapy	Apoplexy, Sheehan syndrome
“Iatrogenic”	Bilateral adrenalectomy, withdrawal from long-term steroid therapy, drugs (mitotane, tyrosine kinase inhibitors)	Hypophysectomy (pituitary surgery), cranial radiotherapy, ipilimumab
“Infants”	Congenital adrenal hyperplasia (e.g. 21 hydroxylase deficiency, 11Beta hydroxylase deficiency), X-linked adrenoleukodystrophy	Genetic mutations e.g. TBX 19, combined pituitary hormone deficiency (CPHD)
“Injury”		Traumatic brain injury

Figure 1: Schematic demonstrating the hypothalamic-pituitary-adrenal (HPA) axis and its disruption in primary vs. secondary adrenal insufficiency



Summary of causes of primary adrenal insufficiency (PAI)

The most common cause of PAI is autoimmune adrenalitis. This is more likely in individuals with co-existent autoimmune disease but also occurs in isolation in up to a third of cases. Addison's disease is found in the monogenic autoimmune polyglandular syndrome type 1 in combination with mucocutaneous candidiasis, hypoparathyroidism and ectodermal dystrophy that is seen in childhood, as well as the more prevalent adult type 2 disease (Kahaly and Frommer, 2017). Thomas Addison originally described the pathological features of adrenal tuberculosis (TB) in 1855 and to this day, TB remains the second commonest cause of PAI in the UK and should be considered in all new presentations of PAI.

Other causes of PAI that may present on the medical take include invasion of the adrenal glands in metastatic disease (usually from primary disease in the colon, lung or breast) and hypoxic injury secondary to hypovolaemic or septic shock. PAI is also seen in rarer syndromes such as antiphospholipid syndrome, congenital adrenal hyperplasia and adrenoleukodystrophy (where very long chain fatty acids can accumulate in the adrenal cortex and also the brain causing neurodegeneration).

Summary of causes of secondary adrenal insufficiency

Secondary adrenal insufficiency refers to a state of adrenal suppression due to insufficiency of adrenocorticotrophic hormone production from the pituitary gland. Pituitary adenomas as well as other sellar tumours such as meningiomas, craniopharyngioma and pituitary metastases may all cause ACTH deficiency and adrenal suppression. Traumatic and blast brain injury are other causes of secondary adrenal suppression (Baxter et al., 2013) as well as pituitary apoplexy and Sheehan's

syndrome in the post-partum period (Table 1). Addisonian crisis is less common in secondary vs. primary adrenal insufficiency due to preserved aldosterone production, which is not under ACTH control, and typically less extensive cortisol reduction.

Drug-related adrenal insufficiency

Patients with established PAI may present to the A&E department in Addisonian crisis having omitted their steroid replacement medication for a variety of reasons. The most common cause is a vomiting illness preventing absorption of corticosteroid. A careful history and/or presence of a medic alert bracelet/card should alert you to this.

An alternative scenario is following cessation of long-term corticosteroid treatment. A 5mg dose of prednisolone (or equivalent) over a 4 week period (topical, inhaled, oral or injected) can cause suppression of the hypothalamic-pituitary-adrenal axis (Bancos et al., 2015) . On cessation of treatment some patients may present in an adrenal crisis. A careful history enquiring as to the use of corticosteroid is warranted, including the use of steroid creams and inhalers. Similarly, patients who have been successfully treated for Cushing's disease or those who may be taking insufficient doses of hydrocortisone whilst on mitotane for adrenal cancer may be particularly vulnerable to an adrenal crisis.

Clinical presentation

A classical Addisonian crisis presents as a shocked patient with electrolyte and metabolic disturbance and a suggestive history. A summary of the history,

examination and laboratory findings typical of an adrenal crisis is presented in Table 2.

Table 2. Summary of potential symptoms, signs and laboratory findings during a suspected adrenal crisis

Symptoms	<p>Weight loss Malaise Pre-syncope or syncopal episodes Confusion Gastrointestinal (GI) disturbance Salt-craving Hyperpigmentation</p>
Examination findings	<p>Hypotension (postural if not in shock) Hyperpigmentation (palmar creases, buccal mucosa, old scars, nipples) Septic source/fever (GI, urine, chest, viral illness) ?MI ?surgical abdomen</p>
Laboratory findings	<p>Hyponatraemia Hyperkalaemia Acute kidney injury from hypoperfusion Normochromic anaemia Hypoglycaemia especially in children.</p>

History

It is important to remember that the majority of patients presenting in adrenal crisis already have a diagnosis of adrenal insufficiency (Hahner et al., 2010). In such patients, it is important to check drug adherence. Patients may have run out of their prednisolone or hydrocortisone, or vomited shortly after having taken it. In new cases of adrenal insufficiency patients or their carers may report non-specific symptoms such as weight loss, malaise, anorexia, nausea, vomiting, abdominal pain, dizziness and joint pain and in PAI more specific symptoms include salt-craving and hyperpigmentation. There may be a history of long-term corticosteroid use that has recently stopped or a history of a pituitary tumour/surgery.

Co-existent autoimmune disease may be present and it is important to ask directly regarding a history of hypothyroidism, type 1 diabetes, vitiligo and autoimmune hepatitis among other autoimmune tendencies including a family history of these conditions. PAI may present with an apparent improvement in glycaemic control in long standing type 1 diabetes or recurrent hypoglycaemia in patients who do not adjust insulin doses accordingly. Metastatic disease should be suspected in those with oncological disease, and tuberculosis should be considered in high risk groups.

Examination

Signs of hypovolaemic shock are usually present (hypotension/tachycardia/cerebral hypoperfusion). Co-existent sepsis may have precipitated the crisis so a careful examination of all systems is necessary. In one survey, vomiting and/or a diarrhoeal illness was responsible for more than 50% of cases of adrenal crisis followed by flu-like illness and associated major infections and surgical procedures. Chest and urine

infections, migraine, allergic reactions, septicaemia, myocardial infarction and hypoglycaemia were other less common causes (White and Arlt, 2010).

In a new presentation of Addison's disease there may be signs of hyperpigmentation due to excessive stimulation of skin melanocortin receptors by high ACTH levels. It is important to look in palmar creases, buccal mucosa, old scars and nipples for signs of increased pigmentation or other areas exposed to mechanical stress.

Initial investigations

Hyponatraemia may be present in primary and secondary adrenal insufficiency and hyperkalaemia in PAI due to mineralocorticoid deficiency. Hypoglycaemia may or may not be present but is more common in children. Thyroid stimulating hormone may be mildly elevated. A random cortisol of <100 nmol/L in a patient with clinical features of an Addisonian crisis is suggestive of adrenal insufficiency and in the 100-350 nmol/L range, adrenal insufficiency cannot be ruled out. Even seemingly 'adequate' cortisol concentrations above this cannot absolutely exclude adrenal insufficiency as they may be inappropriately low for a critically ill patient. Because cortisol is a diurnal hormone, it is also important to bear in mind that healthy individuals often have low afternoon cortisol levels and random cortisol levels can be misleading. However a blood sample before any steroid is administered can be very informative and a sample should ideally be sent for ACTH and cortisol with the electrolytes before any treatment is administered for later review. If adrenal crisis is suspected clinically then immediate management should be instigated before cortisol and ACTH results are available.

Clinical Management

The diagnosis of an adrenal crisis should be made on clinical grounds initially. If the patient is severely unwell then potentially life-saving hydrocortisone treatment should be instigated immediately, without waiting to confirm the diagnosis biochemically. If the patient is haemodynamically stable then it may be reasonable to consider performing a short synacthen test prior to commencing hydrocortisone treatment.

Emergency management (0-24 hours) (Box 1.)

Hydrocortisone (immediate bolus injection of hydrocortisone 100mg i.v. or i.m. followed by continuous intravenous infusion of 100mg hydrocortisone over 24 hrs or 4.2mg per hour). An alternative regimen would be 50mg every 6 hours (i.v. or i.m.) (Arlt, 2016).. The plasma cortisol profile is smoother with an IM bolus compared to IV due to the short half-life of cortisol.

Fluid resuscitation should be with isotonic saline solution. The first litre should be given over 1 hour followed by 4-6 hourly. Monitor for signs of fluid overload.

Top Tips Box 1. Emergency management of an adrenal crisis

- 1) Hydrocortisone 100mg bolus (i.m or i.v)
- 2) Followed by continuous intravenous infusion of 100mg over 24 hours. Or hydrocortisone 50mg every 6 hours i.m or i.v
- 3) 1000ml normal saline over 1 hour
- 4) Followed by 4-6 L normal saline over 24 hours (caution in elderly and those with potential cardiac failure).

On-going management

Specialist endocrine input should be sought at the earliest opportunity to guide on-going management and further investigations. A switch to oral hydrocortisone or prednisolone should be undertaken as soon as the patient is able to eat and drink. The

most common replacement dose of hydrocortisone is 10mg on waking, 5mg at noon and 5mg at 4pm. The dose can be adjusted if necessary in the endocrine clinic. Steroid replacement at these physiological doses does not need to be taken with food.

An alternative may be to consider a once daily dose of prednisolone (2-5mg) and this is a focus of ongoing research (EL. Williams, 2016 , Smith et al., 2017). This may be a preferred option for patients who find thrice daily hydrocortisone difficult to remember and where once daily prednisolone may be a better option for them.

Dexamethasone does not have a role in the long-term treatment of adrenal insufficiency.

In the long run, it is important to remember that excessive steroid replacement is also a cause of increased morbidity and mortality(Hammarstrand et al., 2017).

Laboratory Investigations

Following initial emergency management the diagnosis of adrenal insufficiency needs to be confirmed or excluded by conducting a short synacthen test. This test provides a supraphysiological stimulus (250 mcg synthetic ACTH) to cortisol production and enables investigation of adrenal reserve. The cut-off for stimulated cortisol at 30 minutes will vary according to the assay used but usually ranges from 450-500 nmol/L(EI-Farhan et al., 2013). A baseline ACTH helps to determine whether the adrenal insufficiency is primary (high ACTH) or secondary in origin (normal or low ACTH). Ideally the test should be performed in the morning, so that baseline cortisol and ACTH can be accurately assessed, although other times are also acceptable since

it is the 30-minute cortisol value which is used to guide management. Endocrine advice should be sought where there is any uncertainty in interpretation.

Top Tips Box 2 – How to perform a short synacthen test.

Contraindications:

Pregnancy, pituitary surgery within 6 weeks, Oral contraceptive pill (OCP) or hormone replacement therapy (HRT).

Preparation:

Final dose of hydrocortisone midday on day before. Stop HRT/OCP at least 6 weeks before test.

Method

- 1) Insert 18-20 g cannula
- 2) 0900 hrs take blood for cortisol (yellow top vacutainer) and ACTH (purple top vacutainer). Send ACTH sample lab immediately on ice. Flush cannula.
- 3) Give 250 micrograms tetracosactride i.m. (ideally) or i.v.
- 4) 0930h: After discarding 5 ml blood, take 3 ml blood for cortisol. Flush cannula
- 5) 1000h*: After discarding 5 ml blood, take 3 ml blood for cortisol. Flush cannula)

Interpretation:

Stimulated plasma cortisol >450-500 nmol/L** (or increment rise >150 nmol/L) = normal response

**Different centres may perform 60 minute cortisol measurement, ** check local lab cut-off.*

Further specialist investigations

If adrenal insufficiency is confirmed, further tests will be determined by whether it is primary or secondary in nature and to seek the underlying cause (Table 1) For PAI, adrenal antibodies are useful to determine an autoimmune aetiology and for secondary adrenal insufficiency, biochemical and radiological assessment of the pituitary is usually required. Thyroid function and glycaemic status should be re-checked when steroid replete and the patient is well, as hypoadrenalism itself can affect thyroid and glycaemic status that can reverse following treatment, or may reveal true autoimmune hypothyroidism or diabetes and the lack of cortisol may have influenced the thyroid and glucose results.

Mineralocorticoid replacement

In PAI there is invariably a need for mineralocorticoid replacement in the form of oral fludrocortisone. This is important to prevent postural hypotension and electrolyte disturbance. At higher doses of hydrocortisone (i.e. >50mg in 24 hours) there is no

need for fludrocortisone as hydrocortisone in these doses possesses sufficient mineralocorticoid activity. It is important to minimise the dose of glucocorticoid to minimise side effects, and to do this there is a requirement for daily fludrocortisone replacement (typically 100 mcg once daily). Fludrocortisone should be commenced by an endocrinologist, either prior to discharge or very soon afterwards in an outpatient clinic. Serum/plasma aldosterone will be low and renin will be high in mineralocorticoid deficiency, hence potassium and renin measurements, along with an assessment of postural blood pressure change, can be used to titrate fludrocortisone dose in the clinic. Most patients need between 3mg and 4mg of prednisolone once daily together with fludrocortisone 100mcg (Smith et al). Hydrocortisone 10mg + 5mg + 5mg daily is an alternative to once daily prednisolone.

Discharge and Follow-up

All patients (and family/carers) with confirmed adrenal insufficiency should be educated about their condition. They should be alerted to sick day rules (*Box 3*) and encouraged to carry a steroid emergency card www.endocrinology.org/adrenal-crisis and/or a medic alert bracelet. All patients should be referred to a specialist endocrine clinic. A discharge check list can be found in *Box 4*.

Top Tips Box 3. Sick Day Rules

1. Double hydrocortisone dose during a febrile illness or one that requires antibiotics or bed rest (ensure patient has additional dose of hydrocortisone so dose can be doubled for at least 7 days)
2. Glucocorticoids may need to be administered either i.v. or i.m. during a vomiting or diarrhoeal illness. The patient (or carer) can be taught to self-administer hydrocortisone. Provide a **Hydrocortisone Emergency Injection Kit** and ensure it always remains in date.

Top Tips Box 4. Discharge Check List

New diagnosis of adrenal insufficiency:

- 1) Is the patient well and taking 15-20 mg hydrocortisone or 2mg to 4mg prednisolone, and in PAI fludrocortisone 100 mg daily?
- 2) Has the patient had a short synacthen test and inpatient endocrine review?
- 3) Has the patient been educated about their condition, given an explanation of sick day rules and given a steroid emergency card?
- 4) Has the patient been referred to the endocrine outpatient clinic?

Established diagnosis of adrenal insufficiency:

- 1) Is the patient well and taking usual dose of hydrocortisone or prednisolone?
- 2) Has the reason for adrenal crisis been explored?
- 3) Have sick day rules been re-discussed?
- 4) Does the patient carry a steroid alert card or have a medic alert bracelet?
- 5) Does the patient have an endocrine outpatient appointment booked?

Key points:

- 1) 'Addisonian crisis' is a life-threatening endocrine emergency that requires early recognition and treatment of the condition.
- 2) Most cases of adrenal crisis are in patients who have established adrenal insufficiency.
- 3) An adrenal crisis is more common in primary vs. secondary adrenal insufficiency due to additional lack of mineralocorticoid.
- 4) When suspected clinically, an adrenal crisis must be treated with prompt hydrocortisone replacement and fluid resuscitation.
- 5) In new suspected cases of adrenal insufficiency, the diagnosis should be confirmed with a short synacthen test prior to discharge.
- 6) If confirmed, patients should be established on oral hydrocortisone (usually 15-20 mg in divided daily doses) or 3-4mg prednisolone once daily.
- 7) All patients should be educated regarding 'sick day' rules and encouraged to carry a medic alert bracelet and/or steroid emergency card.
- 8) All patients should be under specialist endocrine follow-up.

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