Module 1765
Cushing's syndrome

From this module you will learn:

- Causes and incidence of Cushing's syndrome
- Diagnosis, symptoms and prognosis
- Management, including glucocorticoid replacement and 5 key cortisol-inhibiting medicines
- The pharmacist's role, including sources of advice and information for patients

October

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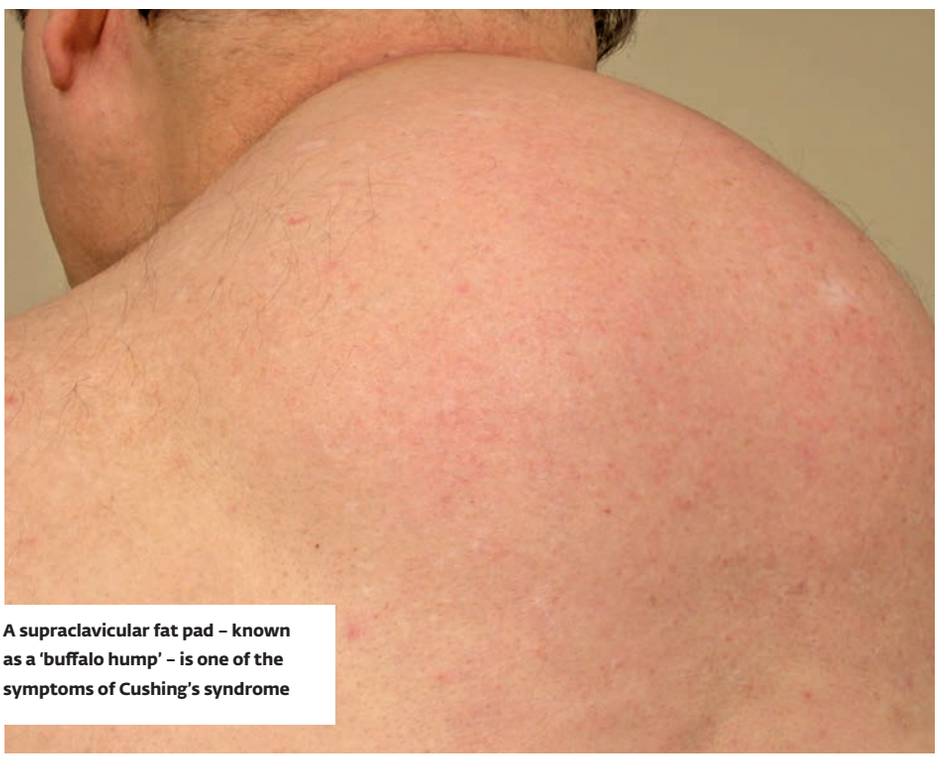
Cushing's syndrome, which was first identified in 1932, refers to a collection of symptoms and physical features resulting from an elevated level of cortisol circulating in the body. It was discovered as a result of pituitary tumours, although it became clear that a similar pattern of symptoms emerges regardless of the cause of the raised levels of cortisol.

Cushing's syndrome affects between 10 and 15 people per million. Occurrence is more frequent in those with diabetes, obesity, hypertension and osteoporosis when compared to the general population. An estimated 2-5% of obese people with type 2 diabetes also have Cushing's syndrome. The peak incidence is between 25 and 40 years of age, and it is three times more prevalent in females than in males.

If not adequately controlled, Cushing's syndrome can have devastating consequences. It increases the risk of dying five-fold, and can also significantly reduce quality of life through its effects on physical and mental health. The condition can affect appearance, cardiovascular risk, behaviour – which may have an impact on relationships, work and education – and overall health.



A supraclavicular fat pad – known as a 'buffalo hump' – is one of the symptoms of Cushing's syndrome

Causes of Cushing's syndrome

In normal circumstances, cortisol plays an important role in homeostasis. In stressful situations, or when blood sugar levels are low, corticotrophin-releasing hormone (CRH) is released from the hypothalamus. CRH stimulates release of the adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which in turn acts on the adrenal glands to produce cortisol. Levels are maintained and controlled by a negative feedback mechanism, which slows ACTH production.

Cortisol, along with adrenaline, is responsible for the body's fight or flight response; in the short term, it is essential to prevent hypotension, shock and death in stressful or traumatic situations. Although primarily a glucocorticoid, cortisol also possesses some mineralocorticoid properties. It is involved in blood pressure maintenance, cardiac function, immune system control, energy production as well as bone formation, sleep-wake cycle control, mood regulation, memory, wound healing and electrolyte balance.

Excess cortisol can either be produced by the body (endogenous Cushing's syndrome), or artificially introduced into the body (exogenous Cushing's syndrome).

Endogenous causes

ACTH-dependent:

- Pituitary tumours (Cushing's disease)
- Ectopic corticotrophin syndrome
  - small-cell lung carcinomas
  - bronchial carcinoid tumours
  - other endocrine tumours

ACTH-independent:

- Adrenal adenomas
- Adrenal carcinomas

Exogenous causes

Long-term corticosteroids:

- Oral corticosteroids
- High-dose inhaled or topical corticosteroids
- Corticosteroid abuse

Diagnosis and symptoms

Symptoms of advanced Cushing's syndrome are characteristic and may be easily recognisable. However, the syndrome can be present to differing degrees depending on the extent and length of exposure to high cortisol. Milder forms of Cushing's may be difficult to spot because symptoms such as fatigue and hypertension can be non-specific and easily confused with other, more common, problems.

There are various tests for Cushing's syndrome *(see above right)*, but none are definitive. One study found that diagnosis takes multiple consultations and about six years on average, during which time the extent of the syndrome progresses and the likelihood of complete recovery reduces. Differential diagnoses include anxiety and/or depression, alcoholism, obesity, poorly controlled diabetes and HIV infection. In the UK, diagnosis is almost exclusively undertaken in specialist secondary care settings.

Cushing's syndrome typically follows a chronic course, with slow progression,

Tests for Cushing's syndrome

General investigations	Full blood count, electrolytes, acid base balance, potassium levels
24-hour urinary-free cortisol	This test provides a picture of the average cortisol production over 24 hours
Low-dose dexamethasone suppression test	Dexamethasone normally suppresses ACTH and therefore cortisol secretion – in Cushing's syndrome there is incomplete suppression
Midnight cortisol levels	An elevated midnight cortisol level is suggestive of Cushing's syndrome
Dexamethasone-suppressed corticotrophin-releasing hormone (CRH) test	Testing CRH levels includes measuring the response to an intravenous bolus injection of synthetic CRH at doses of 1mcg/kg of body weight

cyclical exacerbations and, rarely, remissions. Symptoms include:

- truncal obesity – patients are heavy or obese above the waist, but with thin extremities
- supraclavicular fat pads – 'buffalo hump'
- a round, red face – 'moon face'
- proximal muscle wasting and weakness
- bone weakening, pain or fractures
- thin, delicate skin, resulting in easy bruising
- distinctive, large, red stretch marks
- acne
- poor wound healing
- loss of libido
- depression and/or anxiety
- mood swings and/or behavioural changes
- fatigue
- hirsutism and irregular or absence of periods in women
- headaches
- thirst and frequent urination
- stunted growth in children.

Perhaps the most detrimental consequences of Cushing's syndrome are increased blood pressure, glucose and cholesterol levels. Sufferers are therefore at increased risk of cardiovascular disease, type 2 diabetes and hypercholesterolaemia. The syndrome has a 50 per cent mortality at five years, mainly due to cardiovascular events. Due to cortisol's immunosuppressive effects, patients are also more at risk of life-threatening infections.

Prognosis is somewhat dependent on the cause of the syndrome, as well as how long it has been left untreated. Most causes are easily reversible, but some symptoms may not be reversible once endocrine cure is achieved. For example, bones may not return fully to their pre-Cushing's strength, some organ damage may be irreversible, and patients will remain at a higher risk of developing diabetes, hypertension, and hypercholesterolaemia.

Management

A key step in recognising and managing Cushing's syndrome is careful history-taking to identify any sources of exogenous cortisol. The patient's medication history – including any herbal medicines, creams and inhalers – should be carefully scrutinised. Oral corticosteroids are the most common cause of the syndrome, but cases have also been reported due to frequent use of high-dose steroid inhalers or skin creams.

If the Cushing's syndrome is iatrogenic, stopping the offending medicine should be all that is necessary to cure it. Prolonged use of excess exogenous steroids means that the usual negative feedback mechanisms end up shutting down the hypothalamic-pituitary-adrenal process that produces endogenous cortisol and suddenly stopping corticosteroid therapy may lead to a life-threatening adrenal crisis. The corticosteroid therefore needs to be withdrawn gradually, through careful tapering. If the original condition that prompted use of corticosteroids still requires treatment, alternative options should be sought. If continued corticosteroid treatment is unavoidable, the lowest dose possible should be used and the patient carefully monitored.

For endogenous Cushing's syndrome, the aims of treatment are to normalise cortisol levels and remove causative tumours while avoiding cortisol deficiency. Surgery tends to be the mainstay of treatment, usually in combination with either chemotherapy, radiotherapy or cortisol-inhibiting drugs.

Pituitary tumours are usually removed through transphenoidal surgery. Where this fails or is contraindicated, pituitary radiotherapy may be used. A course of radiotherapy can take one to three years to take effect. Adrenal tumours may be removed through adrenalectomy, and this can also be done in cases where pituitary surgery fails to control high cortisol levels. If Cushing's syndrome is caused by an ectopic source, treatment of the original cancer by surgery or chemotherapy should be sufficient to correct it.

Glucocorticoid replacement therapy is usually required for at least nine to 12 months after surgery. For rare cases, such as where the entire adrenal gland is removed or the pituitary gland is damaged, lifelong replacement may be required. Of the available steroids, hydrocortisone is the treatment of choice because it most closely resembles endogenous cortisol. The usual dose is between 10 and 50mg daily. Doses are individualised and tend to be split throughout the day to maintain adequate amounts while matching the natural variations in levels. Larger doses are given in the morning, with smaller doses usually at lunchtime and teatime. Natural cortisol levels reach their lowest point at about midnight so – to avoid insomnia – hydrocortisone doses should be taken no later than 6pm.

Cortisol-inhibiting medicines act to decrease production of cortisol in the adrenal gland. They may prove useful either alone in the management of mild Cushing's syndrome or in combination with other strategies in the treatment of more severe illness. They are generally considered specialist drugs and should be initiated and managed through secondary care specialist endocrine services. Most are licensed as designated orphan products – drugs developed specifically to treat a rare medical condition – and, as such, there is little good quality evidence available.

Because patients with Cushing's syndrome are more susceptible to infections and poor wound-healing, cortisol-inhibiting medicines can be particularly useful in the run up to surgery to reduce the likelihood of post-operative complications. Options include mitotane, metyrapone and ketoconazole. Mifepristone and etomidate are also used occasionally.

- **Mitotane** is an adrenal cytotoxic drug licensed for the symptomatic treatment of advanced adrenal cortical carcinoma. Its exact mechanism of action remains unknown. It is dosed according to plasma levels and requires close monitoring. Gastro-intestinal adverse effects occur in 10-100% of patients, but can be easily treated with dose reductions. More serious adverse reactions include hepatotoxicity, tumour infarction and haemorrhage, brain damage and leucopenia. Its onset of action can be delayed, but it may retain its effectiveness for a long period of time.
- **Metyrapone** is an enzyme inhibitor that blocks biosynthesis of cortisol and aldosterone. It is licensed both as an aid to diagnosis of Cushing's syndrome as well as in its treatment. Dosages should be adjusted on an individual patient basis, with usual doses ranging from 250mg to 6g daily in three to four divided doses. It may be used to normalise cortisol production, or as part of a block-and-replace regimen. Long-term use can result in hypertension due to accumulation of desoxycorticosterone. Other side effects include allergic skin reactions, hypoadrenalism, hirsutism and drowsiness.
- **Ketoconazole**, better known as an antifungal agent, acts in a similar way to metyrapone to block the final stage of cortisol production. It also has anti-androgenic properties, which make it particularly useful in female patients with hirsutism but limits its use in male patients. Ketoconazole also inhibits synthesis of LDL cholesterol. It is licensed in a tablet formulation for the treatment of endogenous Cushing's syndrome in adults and adolescents aged 12 years and over. Doses required to treat Cushing's syndrome are higher than those used for fungal diseases, with usual maintenance doses falling in the ▶

region of 400-1,200mg daily in two to three divided doses. Absorption can be variable, and patients should be advised to take it with food or an acidic drink such as cola. Oral ketoconazole can cause serious hepatotoxicity and QT interval prolongation, so patients require careful monitoring. It also has the potential to interact with a wide range of medicines because it is a substrate for the inhibitors of cytochrome P450 enzymes.

- **Mifepristone**, a glucocorticoid and progestin-receptor antagonist, is licensed as an abortifacient. It is sometimes used to counteract hypercortisolism prior to surgery or before the initiation of radiotherapy. It is taken orally at an initial dose of 200mg twice daily or 6mg/kg/day. It can then be gradually titrated up to a maximum of 25mg/kg/day according to response. Patients need to be carefully monitored because it can cause adrenal insufficiency and hypokalaemia.
- **Etomidate**, an anaesthesia induction agent, is sometimes used off-label to treat Cushing's syndrome in seriously ill patients with pituitary tumours or ectopic corticotrophin syndrome. It acts similarly to ketoconazole, but with less antiandrogenic effects and a more potent anti-cortisol effect. It is only available as an intravenous product, which limits its usefulness. It is usually used for no longer than seven days.

The pharmacist's role

Community pharmacists can play a pivotal role in preventing and detecting cases of Cushing's syndrome. Pharmacists see many patients who are on long-term steroid therapy for organ transplants, asthma, arthritis and inflammatory bowel disorders. Medicines use reviews present a perfect opportunity to check the appropriateness of an ongoing prescription and to ensure the patient is taking the lowest possible dose required.

Patients may also present to the pharmacy for advice on treating symptoms that may be indicative of Cushing's syndrome. Pharmacists are therefore well-placed to advise patients to seek endocrine referral if Cushing's syndrome is suspected. They can also provide advice to those taking cortisol replacement therapy.

As with most chronic diseases, patients may struggle to cope and adjust to their illness. The pharmacist can guide patients to the most reliable, evidence-based sources of advice and information. NHS Choices, the Patient website and Medline Plus all have good, easy-to-understand information about Cushing's syndrome, including for adolescents and teenagers. The Pituitary Foundation also provides online information, as well as local support groups, patient forum, peer-to-peer telephone service and email support.

References

- Medline Plus Health Topic: Cushing's Syndrome. www.nlm.nih.gov/medlineplus/cushingssyndrome.html
- Tidy, C. Professional References: Cushing's Syndrome. Patient.co.uk 2015: patient.info/doctor/cushings-syndrome-pro
- NHS Choices: Cushing's Syndrome. www.nhs.uk/conditions/Cushings-syndrome/Pages/Introduction.aspx
- Prague J, May S and Whitelaw B. Cushing's Syndrome. BMJ 2013; 346:f945
- Falade J. Management of Cushing's Syndrome. Pharmaceutical Journal 2011; 287: 395-398

5-Minute Test

1. An estimated 10% of obese people with type 2 diabetes also have Cushing's syndrome.
True or false?

2. Cushing's syndrome is three times more prevalent in women than in men.
True or false?

3. Cortisol is involved in many body functions including blood pressure maintenance, cardiac function, immune system control and energy production.
True or false?

4. Causes of exogenous Cushing's syndrome include pituitary tumours, ectopic corticotrophin syndrome and adrenal carcinoma.
True or false?

5. Symptoms of Cushing's syndrome include truncal obesity, a round, red face and proximal muscle wasting and weakness.
True or false?

6. Patients with Cushing's syndrome have an increased risk of cardiovascular disease, type 2 diabetes and hypercholesterolaemia.
True or false?

7. Cushing's syndrome is associated with 75% mortality at five years.
True or false?

8. Hydrocortisone should be taken in a single dose at night to match the natural variations in levels.
True or false?

9. Metyrapone is an enzyme inhibitor that blocks biosynthesis of cortisol and aldosterone.
True or false?

10. Ketoconazole has less anti-androgenic side effects than etomidate.
True or false?

Tips for your CPD entry on Cushing's syndrome

Reflect **Which conditions increase the risk of developing Cushing's syndrome? How is Cushing's syndrome tested for? What are the side effects of cortisol-inhibiting medicines?**

Plan **This article describes Cushing's syndrome and contains information about its causes, diagnosis, symptoms and management. The role of the pharmacist in preventing and detecting potential cases is also discussed.**

Act **Read the Update article and the suggested reading (below). Update and Update Plus subscribers can then access a 5-Minute Test and a pre-filled CPD logsheet at chemistanddruggist.co.uk/mycpd.**

Read more about Cushing's syndrome on the Patient website
tinyurl.com/cushings1
tinyurl.com/cushings2

Revise your knowledge of corticosteroid use from the *BNF* Section 6.3 Corticosteroids

Identify any patients taking long-term corticosteroids who may be at increased risk of Cushing's syndrome or who might benefit from an MUR or more information in a patient consultation

Find out about organisations that offer support for patients with Cushing's syndrome such as The Pituitary Foundation
tinyurl.com/cushings3

Find out about any local support groups

Evaluate **Are you now confident in your knowledge of Cushing's syndrome? Could you advise patients and carers on its management?**

Expert Q&A

Want to know more? Our Cushing's syndrome expert is on hand to answer any further questions you may have. Email: **asktheexpert@updateplus.co.uk**