A GUIDE TO

CUSHING'S DISEASE

Australian Pituitary Foundation

INCIDENCE

Approximately 41 people are diagnosed with Cushing's disease every year in Australia. This represents around 0.16 new cases per 100,000 population per year[1].

PREVALENCE

Between 300 and 1,600 Australians currently live with Cushing's disease. This represents around 1.2-6.4 cases for every 100,000 population[2,3].

ABOUT CUSHING'S DISEASE

Cushing's disease is a rare condition that occurs when the body produces too much of the steroid hormone cortisol. This happens as a result of a pituitary tumour producing excessive amounts of the pituitary hormone adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal glands to produce excessive amounts of cortisol. Cortisol is the main hormone that helps your body deal with stress (such as injury or infection) and controls blood sugar levels. Occasionally, the ACTH-producing tumour can be located somewhere else in the body. This is referred to as an 'ectopic tumour'.

Cushing's disease specifically refers to the condition of excessive ACTH production by a pituitary tumour. **Cushing's syndrome** however is the term to describe the condition of excess cortisol in the body which can be due to Cushing's disease or other causes such as long-term use of corticosteroid medication, severe depression, excessive alcohol use or a tumour on the adrenal gland that produces the hormone cortisol.

PRESENTING SIGNS AND SYMPTOMS

Cushing's disease can be difficult to diagnose as some of the symptoms are very common in the general population and occur with other medical conditions. Further, symptoms and signs can develop slowly over long periods of time, making Cushing's disease even harder to recognise.

Physical symptoms

- Thin, fragile skin that tends to bruise easily
- Stretch marks – red/purple streaks across the skin
- Muscle loss and weakness
- Weight gain, particularly around the waist
- Increased fat on back between the shoulders (a 'hump')
- Face appears round
- Irregular or no menstrual periods (in women)
- Hirsutism- excess growth of facial and body hair (in women)
- Reduced growth (in children)
- Infertility (men and women)

General symptoms

- Fatigue
- Impaired Quality of Life
- Impaired school/work performance

Emotional Changes

- Depression
- Anxiety
- Unable to think clearly
- Mood and behavioural changes- personality traits can become more intense
- Increased irritability

Other conditions or complications often seen with Cushing's disease[4]

- Osteoporosis
- Fractures
- High blood pressure
- High blood glucose/Diabetes
- Infections
- Depression

INVESTIGATIONS

No single test is 100% able to diagnose Cushing's disease. Therefore a combination of tests is required which can include:

- Blood test - to measure hormone levels, including ACTH and cortisol
- 24-hour urinary free cortisol test - to measure daily cortisol production
- Late night or midnight salivary cortisol test - to check for loss of daily cortisol rhythm
- Overnight dexamethasone suppression test - to see if cortisol production can be suppressed
- Magnetic resonance imaging (MRI) or computed tomography (CT) scan - to see the pituitary gland (and, sometimes, the adrenal gland)

For some patients, a few other tests are needed including:

- Inferior petrosal sinus sampling (IPSS) - to check whether ACTH is being released from the pituitary gland or elsewhere
- Visual field test - to check for any loss of vision
- Bone mineral density (BMD) test - to check bone health.

If the results indicate Cushing's syndrome rather than Cushing's disease, further tests may be needed to find the source of the high cortisol levels. These are usually organised by an endocrinologist. Around 1 in 6 people (15%) with Cushing's disease have cyclical Cushing's syndrome[5]. This means they rotate between periods of normal and high cortisol production. This means that results can appear normal, depending on when the tests are performed in the cycle. Repeated tests may be necessary to catch a period of high cortisol production.

TREATMENT

The goals of treatment for Cushing's disease are to restore cortisol to normal levels, reverse symptoms and improve quality of life[6]. This generally requires removing (or controlling the growth of) the pituitary tumour, while maintaining the function of the pituitary gland. Treatment decisions will be tailored to the individual patient, and will depend on a number of features, including the patient's age, gender, the size and location of the pituitary tumour, hormone levels, other medical conditions, current medications, desire for conception, and potential benefits and side effects of treatment. Treatment possibilities include:

1. **Surgery -** to remove the pituitary tumour. Transsphenoidal surgery is performed in most cases.
2. **Radiotherapy -** may be required where surgery is not possible or does not reduce cortisol levels.
3. **Medication -** to control cortisol levels.
4. **Bilateral adrenalectomy** (removal of the adrenal glands) – used rarely only when surgery and radiotherapy are not possible.

Medication may be used to reduce high cortisol levels before surgery, between surgery and radiotherapy, and/or while waiting for radiotherapy to take effect. Medications fall into three general categories:

- Medications that stop the adrenal glands from producing cortisol (ketaconazole, metyrapone, mitotane)
- Medications that prevent the pituitary gland from releasing ACTH (cabergoline and pasireotide)
- Medications that block the action of cortisol around the body (mifepristone)

These can be taken alone or in combination.

AFTER SURGERY

There are several possible outcomes following surgery.

- Cortisol levels can remain high (referred to as 'hypercortisolaemia'). If this occurs, repeat surgery or an alternate treatment option will be considered based on individual characteristics.
- Cortisol levels can be in a normal range (referred to as 'eucortisolaemia'). If this occurs, your doctor will monitor your cortisol levels as they may change over time.
- Cortisol levels can be low (referred to as 'hypocortisolaemia'). Low cortisol levels are the best indication of a successful surgery, as it means the source of increased cortisol had been removed. This requires treatment with cortisol replacement medication (also referred to as steroid therapy). This dose is typically reduced over 6-12 months, however in some cases, cortisol replacement is required longer term. If stopped too early or too quickly, this can have adverse side-effects.

The hormone changes that occur after a successful surgery can make many patients feel worse and even develop new symptoms, such as nausea, fatigue, depression and anxiety. This is caused by cortisol withdrawal, even if using cortisol replacement medication. Recovery can sometimes take a year or longer. Your doctor should give you written advice about cortisol replacement/steroid therapy and the need to adjust the dose of this medication when stressed or ill. Wearing a medical alert bracelet/tag and carrying instructions for emergency steroid treatment is essential. It can take months for weight, depression, strength, fatigue and mood to return to normal.

LONG-TERM OUTCOMES

Long-term monitoring is necessary to ensure pituitary function and hormone levels stay in a normal range, and to identify tumour regrowth and/or adjust medication as required. An ongoing concern for those whose Cushing's disease is in remission, is that there is a high rate of recurrence of the condition. For this reason, long-term follow up is strictly required for all people with prior Cushing's disease.

Surgery can result in 'hypopituitarism' – a condition where the pituitary gland is unable to produce other pituitary hormones. If this occurs, long-term hormone replacement therapy will be required. Radiotherapy may also result in long-term hypopituitarism, which can arise many years after the radiotherapy treatment.

Seeking professional advice and support for management of psychological symptoms is strongly recommended. Following a suitable diet and taking part in regular exercise can help control weight gain.

COMMON QUESTIONS

Why am I putting on weight?
Cortisol has many functions in the body, including converting proteins, carbohydrates and fats into energy. If this energy isn't needed, it becomes stored as fat. High levels of cortisol in Cushing's disease can lead to a progressive accumulation of fat.

Why am I so moody?
The excess hormone produced by the tumour has a direct effect on the brain. It tends to produce dramatic mood swings.

Why am I getting facial hair?
The pituitary hormone, ACTH, stimulates the adrenal gland to produce androgens, which promote facial hair growth.

Why do I bruise so easily?
Cortisol increases breakdown of tissue proteins. This causes weakening of the tiny blood vessels near the skin (capillaries), meaning they break easily and cause bruising.

Why have I developed stretch marks?
Cortisol causes increased breakdown of proteins in the skin, which makes the skin more fragile.

Why do I feel so weak?
Too much cortisol causes the increased breakdown of proteins. One effect of this is muscle wasting, which mainly affects muscles in the upper arms and thighs. This can make it difficult to climb stairs or stand after sitting. Extra weight can also put strain on your muscles, particularly those in your back, sometimes causing back pain and fatigue.

Will I be completely cured after treatment?
In most cases, treatment is successful and usually leads to remission of disease. However, sometimes Cushing's disease can recur. This is why regular follow-up appointments with your endocrinologist are important. Even if you are not cured, most patients find the symptoms improve with treatment.

Is Cushing's disease inherited?
Most cases of Cushing's disease have no inheritance pattern. It has been reported very rarely in families.

MORE INFORMATION

The Australian Pituitary Foundation provides social support for patients and carers, and has published a range of patient resources on pituitary conditions and treatments. For more information, or to join or donate to the APF, please visit our website: www.pituitary.asn.au

Email: support@pituitary.asn.au
Phone: 1300 331 807

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