



Information for patients and their families and friends

Cushing's syndrome

Appendix to the 'Quality of Care Standard for Adrenal disorders in the Netherlands'

Introduction

This informative brochure is intended for people who have Cushing's syndrome and also for their families and friends. Youngsters and adults with Cushing's syndrome will be able to use this brochure independently. But if you are the father, mother, brother, sister or partner of a child or adult with Cushing's syndrome, it can be very useful to gain more insight into the disorder and how it affects patients.

We use the pronoun 'you' in this brochure to address both Cushing patients and the carers, families and friends who come into contact with them. Welfare workers will also find this brochure useful.



The medical content of this brochure is based on the 'Quality of Care Standard for Adrenal disorders' (2018), the guidelines 'The diagnosis of Cushing's syndrome' and 'Treatment of Cushing's Syndrome', both from the Clinical Practice Guideline series published by the Endocrine Society.

This information is not intended to replace the advice of a competent physician. If you have any queries or need advice, get in touch with your GP or your specialist.

This brochure describes the Dutch situation. Please check with your local healthcare professional if and how this can be applicable in your situation outside the Netherlands

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Say hello to ...
Ayisha
aged 21

She has Cushing's syndrome. For the past six months she has been living in student accommodation and studying Educational Sciences in Utrecht. Ayisha comes from a close-knit family and has two brothers. Her mother always took good care of her and regulated her medication. That caused the occasional argument! Ayisha wants to LIVE and her illness sometimes gets in her way.

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The Hypothalamic-Pituitary-Adrenal (HPA) axis

Cushing's syndrome presents a very complex clinical picture. To properly understand what actually goes wrong, it is important that you understand the basics of how hormones work. That is what this paragraph is about. We will explain about the hypothalamic-pituitary-adrenal - or HPA - axis.

The HPA axis

Everyone has one. It's a system that connects the hypothalamus, the pituitary gland and the adrenal glands.

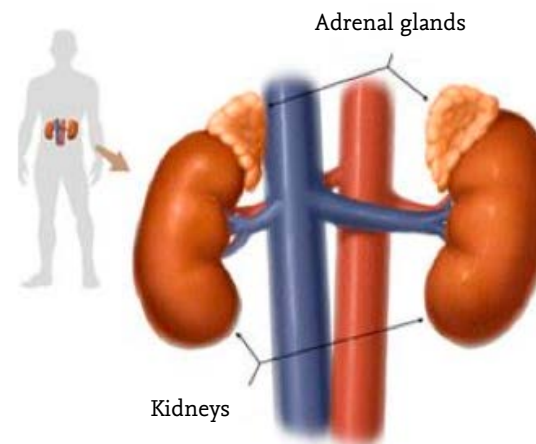
HPA is the English abbreviation of 'hypothalamic-pituitary-adrenal axis'.

The signals that are produced by those organs through hormones belong together and are referred to, together, as the hypothalamic-pituitary-adrenal system. In short: the HPA axis.

The system consists of three components:

- the hypothalamus
- the pituitary gland
- the adrenal glands.

The hypothalamus and the pituitary gland are located in your head; the adrenal glands lie at the back of the abdominal cavity (your tummy).



The adrenal glands sit on top of the kidneys, just like hats.

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Hypothalamus

The hypothalamus lies just above the pituitary gland. It plays an important part in the day-to-day functioning of your body (e.g. regulating body weight, body temperature and fluid balance), and it sends instructions to the pituitary. Hormones can relay signals. The hypothalamus continually measures hormone levels in the blood. If it discovers that there is not enough cortisol, for example, it will send an instruction to the pituitary gland using the hormone CRH. CRH is the natural stimulus for the pituitary gland to produce another hormone, ACTH.

Pituitary gland

The pituitary is a small organ, the size of a pea, that lies at the base of the brain. It plays a central role in regulating the production of various hormones in the body. The pituitary gland itself contains hormone-producing cells.

When they receive instructions from the hypothalamus, these cells produce hormones such as ACTH and TSH. ACTH travels to the adrenal glands via the blood, and once there it stimulates the adrenal glands to produce cortisol.

Adrenal glands

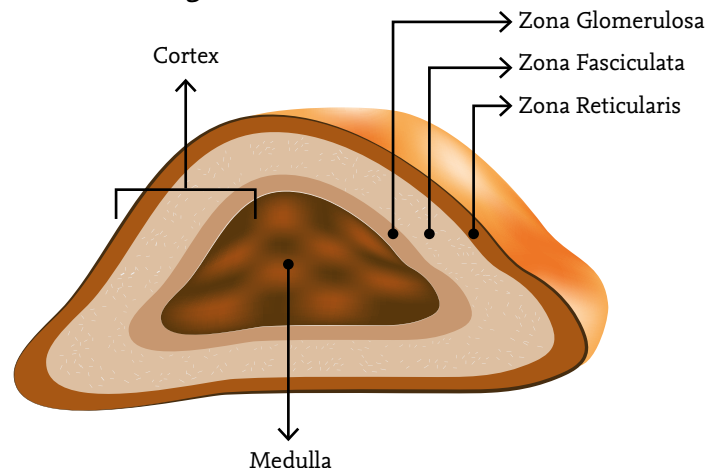
The adrenal glands sit on top of the kidneys in the abdominal cavity. The kidneys are part of the renal system, the adrenal glands are adjuncts to the kidneys - hence their name. Everyone has two adrenal glands, one on each kidney, right and left. Healthy adrenal glands are about the size of your thumb.

Each adrenal gland consists of two components:

- The outside, called the cortex
- The inside, called the medulla.

The cortex is in turn made up of three layers: These layers are called:

- the zona reticularis
- the zona fasciculata
- the zona glomerulosa.



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The various hormones are all produced within these three layers. Hormones are essential to our lives and they regulate everything our body does in different circumstances. The following hormones are produced in the cortex:

- cortisol
- aldosterone
- androgens (sex hormones)

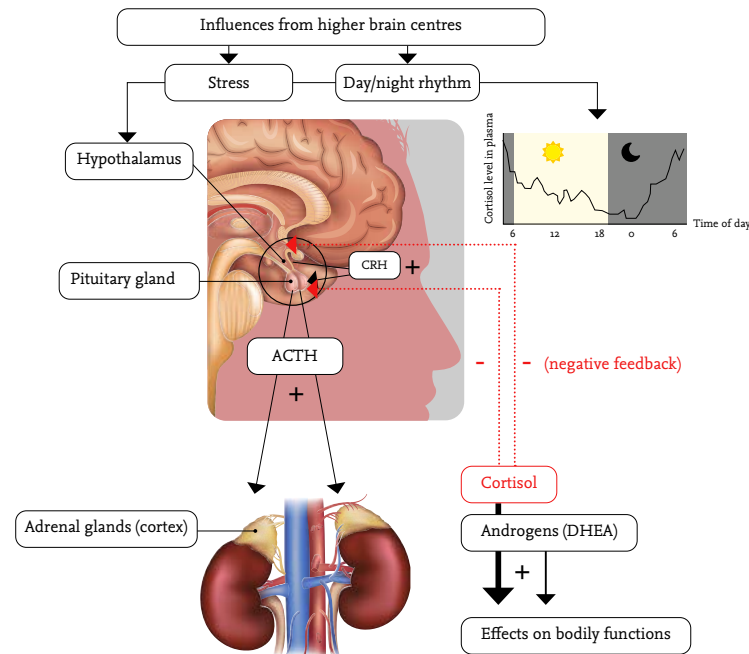


Diagram of the HPA axis



The function of the adrenal glands is explained in more detail on the [website](#).

There is a certain rhythm to the hypothalamic-pituitary-adrenal system. The hormones are released in pulses. The strength of the pulses decreases as the day progresses. That means that our adrenal glands produce a lot of cortisol in the morning, less towards the evening and none (or hardly any) at night. This system is complicated; it varies from person to person and it needs to be very precise. This makes it very difficult to replicate the system using medication.

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What is Cushing's syndrome?

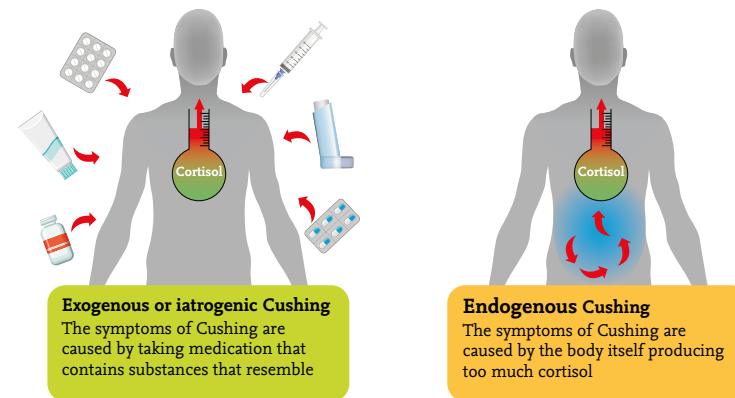
Cushing's syndrome is a disorder that is characterised by a range of signs and symptoms which are caused by an excess of the adrenal hormone 'cortisol' in the blood. This can make you feel ill.

Cortisol

Everyone needs cortisol. It has some important tasks. It influences our sleeping-waking rhythm, our memory, our ability to concentrate and our mood. In addition, cortisol affects the metabolism of sugar, fats and proteins. This makes it possible to make sure that our body has enough fuel when it needs it. Cortisol affects the functioning of our heart and our blood circulation, our bones, skin, connective tissue, muscles and joints. It also has an important role in the body's natural defence mechanism against infection. Cortisol is often called the 'stress hormone'. When you experience physical or mental stress, the adrenal glands produce extra cortisol so that you can recover from the stressful situation. The production of cortisol returns to normal levels once the stress goes away.

Different forms of Cushing's syndrome

Cushing's syndrome presents a very complex clinical picture and it occurs in a number of different forms.



Two forms of Cushing

Exogenous or iatrogenic Cushing can occur as the result of using medication that contains cortisol or substances that resemble cortisol. Examples of such medication are skin creams, inhalation medication or injections.

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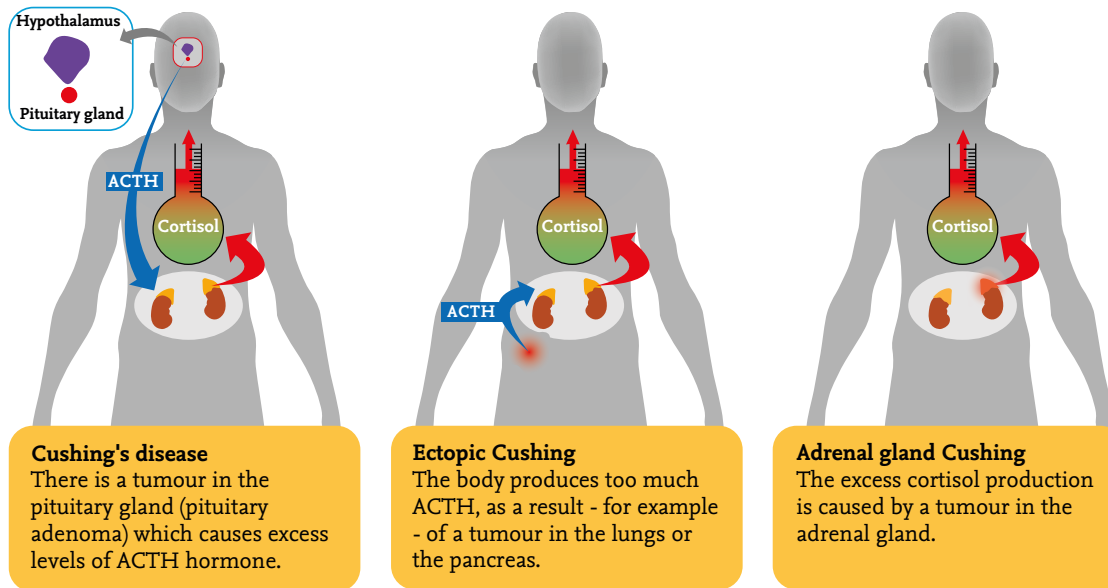
In the case of endogenous Cushing, the excess cortisol in the blood is due to too much cortisol being produced by the adrenal glands.

Endogenous Cushing can further be divided into different categories, as can be seen in the illustration below.

In the case of Cushing's disease (on the left), the problem is caused by a pituitary adenoma. This adenoma produces too much ACTH hormone. ACTH stimulates the adrenal glands to produce adrenal hormones, including cortisol.

The adenoma is nearly always benign. A benign growth of this type is called a pituitary adenoma. The disorder was discovered by an American neurosurgeon called Harvey Cushing. This is the reason that the pituitary form of Cushing is called 'Cushing's disease'.

In the case of ectopic Cushing (in the middle, below), the problem is caused by a benign growth somewhere other than the pituitary, perhaps in the lungs or the pancreas. This growth leads to the production of too much ACTH or CRH hormones, either of which will stimulate the adrenal glands to produce too much cortisol.



There are three forms of Endogenous Cushing

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In the case of Adrenal Cushing (right-hand illustration, above), the cause is a benign or malignant growth in the adrenal gland. This growth produces too much cortisol.

Cyclic Cushing's syndrome

There is one more special form of Cushing's syndrome: cyclic Cushing's syndrome. Cyclic Cushing is a special form of Cushing's syndrome, whereby periods of increased production of cortisol alternate with periods without increased production. The time between two periods of excess cortisol production varies from patient to patient. For some patients weeks can go by between the periods of increased cortisol production while other patients have them more frequently.

Different treatments are used for the various forms of Cushing's syndrome. It is therefore important that you ask, and understand, which form you have.



The infographic 'What is Cushing's syndrome' and the animated clip (Dutch only) with the same name provide a further explanation of what Cushing's syndrome entails.



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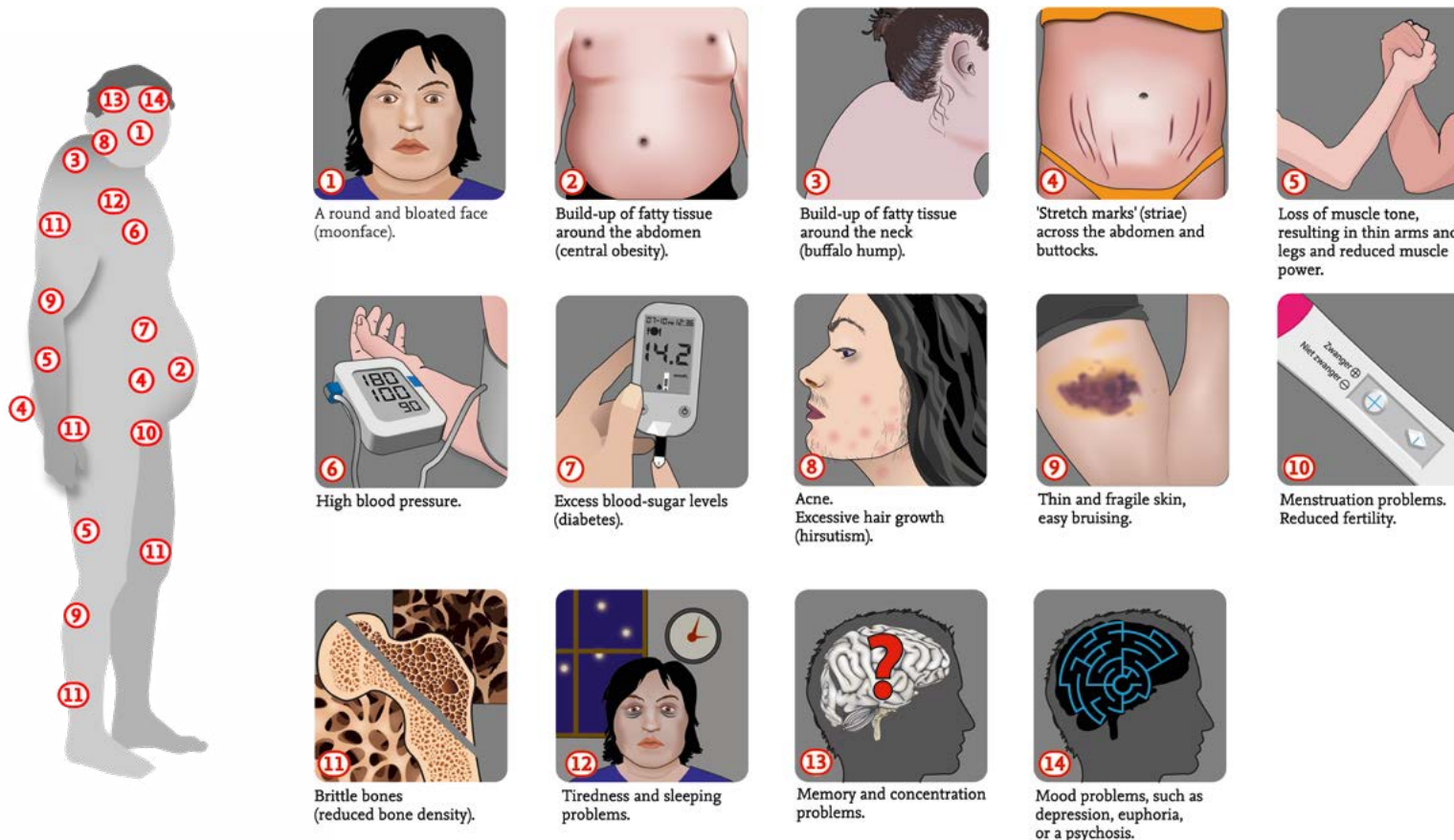
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What are the symptoms of Cushing's syndrome?

Too much of the hormone cortisol in the blood causes a wide range of symptoms. Symptoms can include:



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What causes Cushing's syndrome?

The most common cause of Cushing's syndrome is the use of medication that contains cortisol or a substance that closely resembles it. It is not entirely clear how frequently this form of Cushing actually occurs. Probably more often than is commonly thought, given the number of patients who are given medication which includes corticosteroids.

In the case of endogenous Cushing, Cushing's disease is the underlying cause in around 70% of cases. Cortisol-producing adrenal tumours and ectopic ACTH-producing tumours occur less frequently (in 20 and 10% of cases respectively). In both cases, the tumours can be benign or malignant. Ectopic production of CRH is even more rare. Cushing's disease can also form part of a genetic syndrome.

It is estimated that around 50 new cases of Cushing's syndrome are diagnosed in the Netherlands each year.

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How is Cushing's syndrome diagnosed?

Delayed diagnosis

It is possible that you have felt unwell or possibly even ill, for some time and that your doctors have not been able to pinpoint the precise diagnosis. This is because the symptoms of Cushing's syndrome are non-specific. This means that the symptoms have no direct link to the diagnosis of Cushing's syndrome. They may resemble the symptoms of a number of other disorders. This makes the diagnosis a treasure hunt, one that often begins with the family doctor. He will refer you to the hospital.

Unfortunately, it is often the case that Cushing's syndrome is only diagnosed after a very long search. It is, after all, a very rare disorder. When the diagnosis of Cushing's syndrome is only made after what - from your perspective - is a very long wait, we speak of a delayed diagnosis. The intervening period is characterised by a great deal of uncertainty and doubt, and in the case of Cushing's syndrome it can even mean that damage can occur to other organs in your body.

Having a fatter than usual stomach in combination with thin arms and legs and fattiness around the neck should be making alarm bells ring by the doctors you visit. Ultimately, the diagnosis is usually given by an endocrinologist or other internal specialist.



Further information can be found on the theme page [Diagnostic delay](#) (Dutch only).

Working it out

The diagnosis of Cushing's syndrome is established in various steps.

Intake interview

First of all, it is necessary to check whether the person in question is taking any medication that contains cortisol or substances resembling cortisol. And in that case, efforts will be made to gradually reduce the medication. After a while, symptoms of Cushing's syndrome will start to fade away.

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If the person is not taking any medication of this type, tests will be done to measure the level of cortisol in the body. This stage can be very awkward. There are so many factors that can affect the level of cortisol in the blood, including poorly medicated diabetes, excessive consumption of alcohol, and severe obesity. Quite often, multiple tests have to be carried out and, if necessary, repeated.

For ladies: It is possible that your doctor will tell you to stop taking the birth-control pill during the test period. The test to measure the cortisol level in the blood can only be carried out 1 to 2 months after you stop taking the pill. The medicines in the pill have to be completely cleared from your body.

Indications for high levels of cortisol

Dexamethasone suppression test

The most common test to confirm Cushing's syndrome is the fairly quick dexamethasone suppression test. This test works as follows.

You take 1 mg of the medicine dexamethasone at 11 pm before going to bed. This medicine suppresses the production of cortisol by the adrenal glands. Next morning, between 8 and 9 am., a blood sample is taken so that the level of the hormone cortisol in your blood can be measured.

If the cortisol level has not dropped sufficiently, this

indicates that the adrenal glands are working too hard. This condition is also known as 'hypercortisolism'. Other medicines can also affect the outcome of the test.

24 hour urine test or saliva test

The level of cortisol can also be determined by measuring the cortisol in urine collected over a 24 hour period, or from a cheek saliva swab taken late in the evening at around 11 p.m. You collect your urine carefully in a special plastic container provided by the hospital. These tests are usually carried out two or more times to increase the accuracy of the results. If the level of cortisol in the urine or in the saliva is too high, this will indicate hypercortisolism.

Hair test

This test entails taking a tuft of hair - close to the scalp - and cutting the hairs into lengths of approx. 1 cm. The level of cortisol in the cut hairs gives an indication for cortisol level over a recent period. This test is mainly used to find out whether the patient has cyclic Cushing's syndrome. In the Netherlands, such tests are only carried out in a specialised medical centre such as the Erasmus University Hospital.

Blood test

Sometimes the cortisol concentration in the blood will be measured at different times of the day.

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The highest levels of cortisol and ACTH are usually found in the mornings, and they reduce in the course of the day. Cortisol follows the same daily rhythm as ACTH. In the case of Cushing's syndrome, this normal daily rhythm is not present.

Additional tests in the case of hypercortisolism

If hypercortisolism is diagnosed, the following step is of particular importance because the reason for the increased cortisol in your blood will determine the treatment.

Measurement of ACTH

The level of the hormone ACTH is measured in the blood.

- **ACTH = low**

If the ACTH level is low, i.e. there is too little of this hormone in the blood, Cushing's syndrome is being caused by a tumour in the adrenal gland. A CT scan will then be taken of the adrenal glands to look for a tumour that might be producing the cortisol.

- **ACTH = high**

If the ACTH level is normal or high, i.e. there is too much of this hormone in the blood, this indicates Cushing's disease (due to a tumour on the pituitary) or ectopic Cushing (due to a tumour in the lungs or pancreas for example).

If the ACTH level is normal or high, additional tests are then necessary to pinpoint the precise cause.

Examples of such tests are:

- a high-dosage dexamethasone suppression test
- a CRH test. This is a test whereby CRH is injected into your blood and then measurements are taken at intervals. This is done while you are lying on a bed so you need to go to the hospital or clinic
- petrosal sinus sampling. This is a special test whereby blood is taken from the area around the pituitary and tested. Sampling means testing, in this case testing a small amount of blood
- MRI scan to see whether a pituitary tumour can be identified
- CT scan so that the organs in your chest and abdomen can be checked
- a PET scan using radioactive tracer isotopes to literally highlight small tumours and any possible spreading.

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Carrying out and processing these tests takes a considerable amount of time. It can easily take 6 months. The tests are carried out carefully, need a certain preparation time and they must also be carried in the correct sequence. A lot of people find it hard to understand why the tests have to be repeated at intervals, and that each new round is associated with new waiting lists. The repetition is necessary if the correct diagnosis is to be established, and this is a complicated and sometimes difficult process that patients and their families find hard to understand. You will need to attend the hospital for some of these tests, but in most cases this will not entail an overnight stay. On the other hand, some hospitals will arrange for you to come in for a week so that all the tests can be carried out one after the other.



The infographic entitled 'What is Cushing' explains what tests are done to diagnose Cushing's syndrome.



The website of the Dutch Association for Clinical Chemistry & Laboratory Testing ([NVKC](#)) provides an overview of the tests that are carried out in the laboratory. Unfortunately, the website is only in Dutch. If you type in the substance that is being tested for in your blood or urine, it provides you with a summary of what the test entails, when it is carried out and what the results mean. If you have any further questions you can contact a clinical chemist via the same website.

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What forms of treatment are available for Cushing's syndrome?

The treatment for Cushing's syndrome depends on the underlying cause. It is essential to bring the production of cortisol back to normal levels. Doctors prefer to surgically remove the tumour (this means an operation). If it is not possible to operate, the treatment will involve medication and, sometimes, radiotherapy.

Treatments

For an operation on the adrenal glands, for example, the surgeon needs to have a good deal of experience and expertise. The preparations for the operation progress according to a standard protocol. Patients with pituitary or ectopic Cushing, in particular, need to take medicine to reduce the level of cortisol in their blood before the operation takes place.

The pre-operative preparation phase for patients with pituitary Cushing can therefore last around three months. Patients with adrenal Cushing may have a slightly different preparation phase. It all depends on the severity of the symptoms and the length of time they have to wait for the operation. Your doctor will discuss the preparations with you in detail.



The infographic '[What is Cushing's syndrome](#)' and [the animated clip](#) (Dutch only) with the same name provide a further explanation of how Cushing's syndrome is treated.



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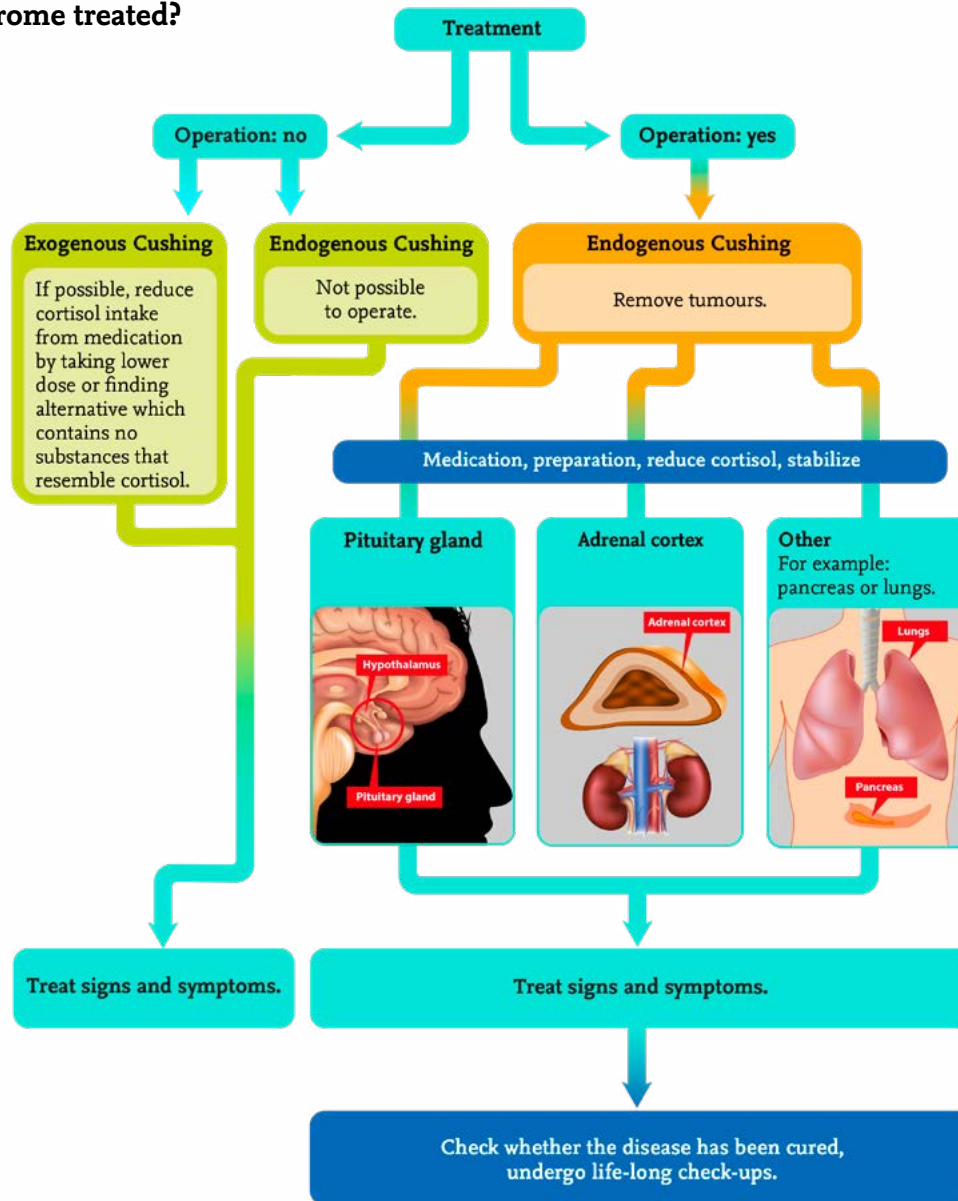
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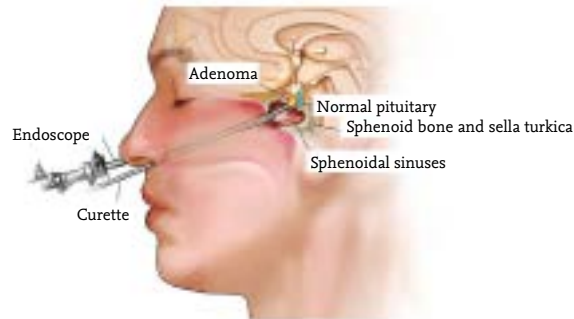
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Surgery

Cushing's disease

In the case of Cushing's disease, the preferred treatment is to remove the tumour in the pituitary gland by way of a transphenoidal resection, an operation carried out through the nose.



This operation is only carried out by the most experienced neurosurgeons.

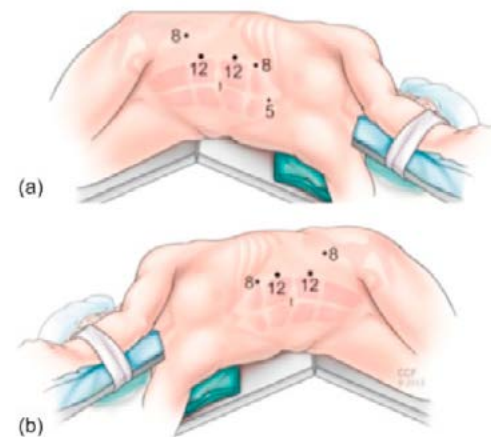
Tumour in the adrenal gland

If Cushing's syndrome is caused by an adrenal gland tumour, the preferred treatment is to surgically remove the tumour. This is usually done laparoscopically (key-hole surgery), while the patient is lying on his stomach.



Ectopic Cushing

In the case of ectopic Cushing, the aim of treatment is to surgically remove the tissue that is producing ACTH or CRH. But it is sometimes very difficult to pinpoint the precise location of an ectopic tumour. Quite often a special scan has to be carried out, whereby the patient is first injected with a radioactive tracer. When a scan is carried out afterwards, the tumour can be localised. The specialist treating you, or the radiologist, will give you further details about this test.



If the root cause of Cushing's syndrome cannot be removed, treatment consists of medication to neutralise the high levels of cortisol in the blood. Alternatively, both adrenal glands might be removed. Radiation (using a Gamma Knife - which is not actually a knife!) is another alternative. It is important that you discuss the various options with your doctor.



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Treating endogenous Cushing with medication

Endogenous Cushing is treated with medication under the following circumstances:

- as preparation for a pituitary operation
- in the case of acute complications arising from severely raised cortisol levels
- if a pituitary operation was unsuccessful or impossible
- in order to cover the period until the radiotherapy becomes effective.

The options for treating endogenous Cushing with medication have increased in recent years. These medicines are divided into three groups:

1. adrenal gland suppressors
2. centrally working medicines aimed at tackling the pituitary tumour
3. medicines that block the effects of cortisol.



Blog: [Study into adrenal gland suppressing medicines \(Dutch only\)](#)

Re 1). Adrenal gland suppressing medicines (such as ketoconazole and metopirone) have been used for several decades. These medicines suppress the production of cortisol by the adrenal gland. Two new adrenal gland suppressing medicines are currently being studied, but they have side-effects such as gastro-intestinal problems and effects on the liver.

Re 2). The centrally working medicines suppress the production of ACTH by a pituitary tumour. The advantage of these medicines is that they directly target the cause of Cushing's disease, namely the problem in the pituitary. Pituitary tumours have certain proteins on the cell surfaces (receptors) and the medicines bind to them. This might be the somatostatin receptor which pasireotide medicine latches on to, or a dopamine receptor, which cabergoline binds to. Pasireotide has been approved for the treatment of Cushing's syndrome in the Netherlands. Although cabergoline is not officially registered, it has been used in treatment for many years.

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Re 3). Medicines that block the effects of cortisol are called glucocorticoid receptor antagonists. The medicine mifepriston is the usual choice from this group.

Mifepriston suppresses the effect that cortisol has on tissues and organs in the body. It works quickly and is particularly used for patients with acute complications from a very excessive level of cortisol.

Patients with moderate to severely raised cortisol levels often need to take a cocktail of medicines to get their cortisol values down. The medicinal treatment is determined for each patient individually, taking into account the severity of the disease, acute complications, possible side-effects and the costs.

The complications of Cushing's syndrome, such as high blood pressure, diabetes and osteoporosis, can be treated adequately with medication.

Support in the period around the operation

The period between the diagnosis and the operation

The period between the time when you hear what's wrong with you and the moment you have an operation can be a very difficult one. And having high cortisol levels doesn't help. These high levels can also have an impact on your emotional well-being. You can feel very down or poorly.

Patients report the following symptoms:

- behavioural changes
- behaving unreasonably towards partner, children, friends and family, for instance
- marriages and other affectionate relationships can be disrupted
- susceptible to psychoses
- being anxious
- being forgetful
- loss of concentration
- patients say that they no longer recognize themselves

It is desirable that patients and their close circle are informed about these symptoms, so that they understand what is happening. It is sometimes necessary to call in support from a welfare worker, nurse-specialist, psychologist or even psychiatrist. Seek professional help if you need it.

The symptoms can also be aggravated by the treatment with cortisol suppressors such as ketoconazole or mitotane. But this is a period that you do need to get through.

Nearly all hospitals provide both oral and written information about the operation and the post-operative period. Ask your specialist about this.



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Preparations for the operation

Generally speaking, the treatment proceeds as follows:

1. The internal specialist establishes the form of Cushing.
2. The internal specialist discusses the plan of action in a multi-disciplinary meeting.
3. The specialist discusses the choice of a particular plan of action with the patient.
4. The specialist refers the patient to the surgeon, who schedules the operation with the departments involved.
5. The surgeon then informs the patient of the plans for the operation.
6. Specialist and surgeon meet the patient and discuss the pre-operative preparations.
7. You meet the anaesthetist and receive information about the anaesthetic and pain management.
8. You receive information about when to come into hospital and what time your operation will be carried out.

As a general rule, your stay in hospital will last between 4 and 7 days. The amount of cortisol in your blood will be measured a week after the operation (earlier, too, if necessary), and the follow-up treatment will be discussed with you. When you leave hospital you will be given instructions for the use of the medicine hydrocortisone. Throughout this period you will be helped and supported by the nurse-specialist or endocrine nurse.

After the operation and the reduction of corticosteroids

After the operation you will mainly be focused on recovering and on reducing your corticosteroids. Patients say that they experience this as a very difficult period. Up to now, they have fixated on the operation with the idea that once it has taken place they will be cured. Unfortunately it is not the operation itself but the recovery after the operation that takes its toll. The body, and that means you, has to get used to not having such high levels of cortisol.

The doctor treating you, or the nurse-specialist, will discuss the reduction schedule with you and give you suggestions that will make life easier. During the post-operative period you should avoid bending down, lifting heavy objects or walking up too many stairs.

Reducing your corticosteroids

An important aspect of the treatment after the operation is the support you receive while you reduce your use of hydrocortisone medicine and the associated symptoms are relieved. After all, your body had become accustomed to higher levels of cortisol. After the pituitary or adrenal adenoma is removed, the production of cortisol ceases immediately. The amount of cortisol in your body is then just about zero. But because cortisol is so important you will be given a substitute, in this case hydrocortisone medicine. In order to encourage the pituitary or the adrenal gland



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to start working again, however, the hydrocortisone needs to be gradually reduced. The idea is that you should not remain dependent on these medicines, so your body needs to be stimulated to produce its own cortisol once again. During the reduction period there will never be quite enough cortisol in your body. As a result, the adrenal gland (or glands) will be stimulated to start working again. You will have just a slight shortage of cortisol in your blood all day.

This can lead to symptoms such as:

- tiredness, lack of energy and vitality, not being able to get anything done
- pain and stiffness in the muscles and joints
- feelings of depression
- nausea, loss of appetite
- generally feeling run down
- sleep problems
- mood fluctuations and cognitive problems.

These symptoms are all part of what is known as the steroid withdrawal syndrome.



Also read the [blog "De zure appel"](#)
(Dutch only)

Reduction can be difficult and sometimes it is not even possible to reduce intake completely. In such cases, patients become permanently dependent on hydrocortisone medicine.

Reduction schedule

The hydrocortisone is reduced gradually, in small steps. How the reduction period progresses, what symptoms subsequently arise and how long the period lasts, varies from patient to patient.

Most patients are able to complete the reduction schedule within 6 to 18 months.

During the final phase of the reduction you are better off reducing the dose in very small steps of just 1 or 2 mg at a time. It is sometimes necessary to take more time for each step.

The best thing to do is to discuss this reduction schedule in detail with your doctor, nurse-specialist or the endocrine nurse.

During the reduction period you will be taking the medication at the agreed times. The reduction of hydrocortisone begins with the evening dose, then the afternoon dose and finally you stop taking the morning dose.

The different hospitals recommend slightly different reduction schedules. Reduction is a very personal process, and rarely follows the schedule originally agreed. It can also be a lengthy process with frequent regression (going back to higher doses of hydrocortisone), and then once more starting to reduce the medication.



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Has the adrenal gland started producing cortisol once more?

During the reduction period, tests will be carried out to check whether the adrenal gland is once more producing cortisol. This can be done in several ways, for example:

At the end of the afternoon prior to the test day, take your last dose of hydrocortisone between 4 and 6 p.m. Next morning, do not take any medication and give a blood sample between 8 and 9 a.m. Take your medication with you, so that you can take it immediately after giving the blood sample. If the adrenal glands have started producing cortisol again, the lab will be able to trace it in your blood.

Help and support

Reducing your medication is not always straightforward. Additional explanations, reassurance and support may well be necessary.

The body, you, needs time to learn to manage with less hydrocortisone. The period with the unhealthy excess of cortisol has come to an end. Under different circumstances we might be speaking of kicking the habit. And sometimes even that is not possible. It could be that it is asking too much of your body, or that your adrenal gland simply doesn't start producing cortisol again.

Some hospitals are now starting to prescribe medication to reduce the production of cortisol by the adrenal glands even before the operation takes place. The medicines used are ketoconazole and metopirone, pasireotide and cabergoline (see page 17).

Severe stress during reduction period

It is, of course, a different story if you experience sudden or severe stress during the reduction period, while the still-drowsy adrenal glands are unable to produce enough cortisol on demand.

In such a case you would need to take extra hydrocortisone for a while, otherwise you run the risk of an adrenal crisis.

An adrenal crisis must be avoided at all costs, or adequately dealt with by means of a high dose of hydrocortisone. But afterwards, once you are feeling a bit better, you must get back down to the dose you were taking (before you had to increase the dose temporarily) as quickly as possible. If you find you need to increase the dose frequently, albeit temporarily, it would be sensible to discuss this with the nurse-specialist or endocrine nurse. You could also consider whether you can do anything about the cause of these stress situations so that you can prevent them occurring in future. Even when you have completely ceased taking hydrocortisone in tablet or capsule form,

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it may be necessary to keep a little of this medication in hand in case of sudden or severe stress. If necessary, you should ask your doctor or specialist for an extra prescription.



What is the Hypothalamic-Pituitary Adrenal system?

Post-reduction testing of the HPA system

You can only be sure that you no longer need to take hydrocortisone medication after the ultimate stress test - either the Insulin Tolerance Test (ITT), the metopirone test or the ACTH test - has been carried out and confirmed that your body is once more producing sufficient cortisol to help you cope with stress.



Read more about the [Insulin Tolerance Test \(Dutch only\)](#) or on [Wikipedia](#).

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Medication

After the operation, your own adrenal glands will not yet be able to produce cortisol. Cortisol is of vital importance in our lives. Given the importance of this medication, it is essential that you have access to an uninterrupted supply of hydrocortisone (or a suitable alternative). You must always have an extra supply of hydrocortisone for use in times of illness or severe stress. If you receive the medication in a Baxter roll, you must also have a quantity that is provided separately in a pot.

The following medicines are commonly used in the Netherlands: hydrocortisone, fludrocortisone and the Solu-Cortef act-O-vial for emergency injections.

Tablets

Hydrocortisone is now only supplied in tablet form in the Netherlands. In the past, doctors, patients, pharmacists and pharmaceutical companies had agreed that the capsules for each of the various doses would have a different colour. Instead of capsules, coloured tablets are now produced and supplied. These tablets are coated to mask the slightly bitter after-taste. Patients had complained that the original white tablets left a nasty taste which lasted for quite some time.

Coated tablets reduce this problem. We recommend that you discuss your medication requirements with your doctor, especially if you experience side-effects.



Further information can be found on the [Theme Page Medication](#) (Dutch only)

Emergency injection

Supplies of the emergency injection (Solu-Cortef act-O-vial) are marked with a 'use by' date. Make sure that this date has not expired. Solu-Cortef act-O-vial needs to be stored at below 25°C, but not in the refrigerator. The prescription will be marked 'manner of use known' or 'use as directed'. You can use 'old' emergency injections to practise preparing an emergency injection. Make sure that your carers practice this as well. It is important that you remain familiar with this skill. The emergency injection is supplied with two syringes and needles. The internal specialist or endocrinologist will give you an extra prescription for the additional hydrocortisone pills to be taken in stressful situations. This prescription will be marked 'Take extra medication as necessary'. [Further information about the use of the emergency injection](#) can be found in the explanation of the adrenal crisis (from page 29).

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Animated clip about the emergency injection.

Fludrocortisone

When both adrenal glands have been removed, you will be dependent on hydrocortisone for the rest of your life, and you will also take fludrocortisone as a substitute for the hormone aldosterone. Aldosterone is the hormone that regulates your salt balance.

Instead of hydrocortisone, your doctor may prescribe a different type of corticosteroid, such as cortisone acetate, prednisone or dexamethasone.

Medication to correct the make-up of your blood in order to treat or prevent cardiovascular disorders or diabetes will be prescribed by the endocrinologist (in consultation with the cardiologist if necessary). A small dose of DHEA will also be prescribed for patients whose DHEA levels are significantly reduced.



Further information about DHEA can be found on the BijnierNET.

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Adrenal crisis and stress instructions

An adrenal crisis is a potentially life-threatening situation for people with adrenal insufficiency.

An adrenal crisis occurs if people with an adrenal insufficiency have to cope with severe stress. You will have a temporary adrenal insufficiency for as long as your adrenal glands are unable to produce enough cortisol under any and all circumstances.

During a stressful moment, your adrenal glands will not be able to produce enough cortisol, while your body needs more. You need to take a medicine, hydrocortisone or cortisone acetate, as quickly as possible. If you are unable to do so, an adrenal crisis could occur.



Read the stress instructions: adrenals.eu/stress-instructions or adrenals.eu/how-an-emergency-injection-works/ or adrenals.eu/stress-instructions/short-instruction-emergency-injection-in-an-adrenal-crisis

If an adrenal crisis threatens, it is important that you do three things:

- The daily quantity of hydrocortisone must be doubled or trebled as set out in the stress instructions.
- When it is not possible to swallow extra tablets, or when they don't have the desired effect, the hydrocortisone must be administered by way of an injection into a muscle or under the skin ([see Emergency Injection](#)) or via an IV drip.
- It is sometimes necessary to administer extra fluids via an IV drip as well.

Your doctor will then carry out tests to establish the cause of the crisis, and treat you further if necessary. When your cortisol levels are too low, this can reduce your ability to make choices such as when to call for help. If they are present, family and friends must step in and call a doctor and/or administer an emergency injection.

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If the necessary measures are not taken promptly, a threatening adrenal crisis can lead to serious symptoms and problems such as reduced consciousness, low blood pressure, disruption to water and salt levels in the body, gastro-intestinal symptoms or even to death. Going through an adrenal crisis, or even the threat of one, can have a lasting impact on your life and increase the anxiety felt by yourself and your family and friends.

The terms Addison crisis and adrenal crisis have the same meaning and are used interchangeably.



The animated clip [Addison crisis](#) (other languages) provides a simplified explanation of the risk of an adrenal crisis and how to deal with it.

The medical specialist or nurse-specialist treating you will give you instructions on how to avoid an adrenal crisis. They will explain how to prepare an emergency injection (Solu-Cortef act-O-vial), how an adrenal crisis might occur and how you can recognize the danger. This is what is meant by the '[stress instructions](#)'.

Stress instructions

The stress instructions help you take the necessary measures. They describe a situation and the changes you need to make (or don't need to make) to the

amount of medication you are taking. In addition, the stress instructions include additional SOS-type measures so that it is more obvious that you are dependent on hydrocortisone. Uniform stress instructions have been drawn up and these have been approved by the Dutch Association for Internal Medicine (NIV) and the Dutch Endocrine Society (NVE). You can download the stress instructions [here](#).

Example situations

Examples of stress situations are:

- illness with fever (high temperature)
- dental treatment
- taking an exam
- having an accident or being in a collision
- attending a funeral

The measures you need to take vary in different circumstances, so you need to consult the instructions you have been given. It is also advisable to make sure that at least one person from your immediate circle knows how to prevent an adrenal crisis. If you are no longer able to prepare and administer the injection yourself, that person will be able to help you and so avoid the long-term problems caused by delay.

Actually experiencing an adrenal crisis can therefore have a significant impact on both you and your family and friends.

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Emergency injection

There are situations in which it is essential to immediately administer an emergency injection of 100 mg hydrocortisone. This would be the case, for example, if you are vomiting or you have watery diarrhoea (your medication will not be absorbed), or if you are only barely conscious.

It is then of vital importance that the injection is administered into a muscle or under the skin. You will receive instructions for this as well, and if you have not already received them it would be advisable to ask your doctor or the nurse-specialist about it.



Animated clip about the [emergency injection](#) (other languages).

If you have had an emergency injection you must always contact your specialist or endocrinologist to talk about what follow-up steps are necessary. Even if your family doctor has administered the emergency injection, it is always advisable to get in touch with your specialist or endocrinologist. The specialist will decide whether you also need to visit the emergency room (A&E) at the hospital.

Visibility and recognition

You are temporarily dependent on hydrocortisone, and for that reason you need to take tablets or capsules. It is possible that you might find yourself in an unexpected situation in which you are unable to communicate your needs adequately. It is therefore important that it should be immediately evident that you are dependent on hydrocortisone.



The following options exist:

- [SOS emergency cards](#)
- [Card holder to attach to car seat belt, shoulder bag, baby seat or buggy](#)
- [In Case of Emergency \(ICE\) contact details on your mobile phone](#)
- [AdrenalAPP on your mobile phone](#)
- [SOS medallion / bracelet](#)
- [Letter from specialist/endocrinologist \(in Dutch and/or English\) to carry when you travel](#)
- [Emergency kit containing emergency medication and written information \(multilingual\).](#)

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Your family doctor can also play a role in the visibility of your condition. Together with the professional association of Dutch GPs and other primary healthcare providers, the Dutch Adrenal Society NVACP has developed a 'disruption flag'. Family doctors are being advised to include this as a 'keep on top' flag in your electronic patient record. This means that when you visit any after-hours GP post in the Netherlands, the duty doctor will immediately see in your record that you are dependent on hydrocortisone.

The specialist or endocrinologist will notify your family doctor about your disorder and explain the stress instructions.

Medical specialists are advised to add a standard sentence at the bottom of each letter to the patient's family doctor, stating that he or she is dependent on corticosteroids and that - in the event of an adrenal crisis or the threat of one - the measures set out in the stress instructions must be taken.

Arrangements have also been made with the Dutch ambulance service so that they know how to act if you need acute care. The National Ambulance Protocol includes measures for acute adrenal insufficiency. It is important that ambulance crews can easily see or recognize that you have adrenal insufficiency.



There are a number of preparations you need to make if you travel abroad. A checklist has been published on the BijnierNET website, under Travel & Holidays (currently only in Dutch). The folder on Adrenal insufficiency and travel (Dutch only) also provides some useful information.



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Residual symptoms and comorbidity

Even after treatment, some people with Cushing's syndrome continue to have symptoms and problems which were caused by the excess of cortisol hormone. During and after the treatment, you should therefore be aware that you may still have some of the following residual symptoms and problems:

- Cardiovascular disorders
 - High blood pressure
 - Glucose intolerance and diabetes
 - Extra weight (difficult to treat)
 - High cholesterol level
 - Increased risk of thrombosis
 - Enlargement of left-hand heart chamber
 - Increased risk of suffering a heart attack
- Symptoms in muscles and joints
 - Pain in the muscles or joints
 - Stiffness
 - Reduction of muscle power
 - Reduced bone density (osteoporosis)
- Psychological and cognitive changes
- Depression
- Anxiety and fearfulness
- Problems with social and inter-personal relationships
- Memory problems
- Attention and concentration problems
- Reduced capacity to cope with stress
- Changes to other hormonal systems as a result of the hypercortisolism or the treatment, for example:
 - Sex hormones (resulting in problems with menstruation or sex-drive, reduced fertility and/or premature menopause)
 - Damage to pituitary because of the operation or radiotherapy, as a result of which the hormone-producing glands no longer receive the right instructions, which can in turn lead to a shortfall in thyroid, growth and sex hormones
- An increased risk of picking up an infection
- Tiredness and reduced vitality

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How is patient care organised?

The care needed by - and provided to - people with Cushing's syndrome is quite complex. This is a rare disorder which results in disabling signs and symptoms that are difficult to associate with a specific diagnosis.

It is important that the disorder is recognized and treated in good time, so that further damage can be avoided. The care for Cushing patients around the time of the operation is highly specialised. In the Netherlands, care is therefore only provided in centres that have an experienced multi-disciplinary

team whose members have a thorough knowledge of Cushing's syndrome. Operations to the pituitary for Cushing's disease are only carried out in a small number of Dutch hospitals.

Check-ups at the out-patient clinic

During every check-up, the endocrinologist or nurse-specialist will pay particular attention to the presence of possible residual symptoms. If necessary, additional tests will be carried out and further treatment given. Attention will also be paid to the impact of these symptoms on your daily life and on the people around you.

After discussing the alternatives with their healthcare professional, some patients opt for a period of extra support and training at a rehabilitation centre. This is not so strange when you realize that you have just been through a difficult time, both physically and emotionally. It is important that you communicate clearly about your needs, and look for a centre that will be able to give you the desired help and support.



Are you looking for a hospital with the necessary experience? Then check out the website of the Dutch Federation of University Medical Centers via the [TRF portal](#). A list of the relevant centres in the Netherlands will be presented. Choose the tab 'Zoek TRF' and type in 'syndroom van Cushing'. A list of the relevant centres will be presented.

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Healthcare checklist

A healthcare checklist has been developed especially for people with Cushing's syndrome. This checklist can help you prepare for your next appointment with the endocrinologist or nurse-specialist. Think of aspects such as:

- Discuss the results of tests (what are the normal values, and what were your results?)
- Check your current medication intake
- Discuss any suspected side-effects or complications arising from the treatment
- Discuss the hydrocortisone reduction schedule
- Have you experienced an adrenal crisis, and how did that work out
- Are you experiencing symptoms, limitations or health problems (either familiar or new)
- Discuss any issues that you are having to contend with and which reduce your quality of life.

- Consider things like memory problems, emotional outbursts, osteoporosis, premature menopause, pain in the joints and infections.
- Information about possible additional tests or new treatments
- Discuss the application of the stress instructions (annually)
- Discuss any problems you experience at work, in other social contexts or within the family
- Ask for extra support you need, including psychological support if necessary
- Ask for information to be provided to your family doctor and, if necessary, to other healthcare providers.

Doctors and nurses are happy to answer these questions, so write them down at home whenever you have time, then you won't forget them during the appointment. Never be afraid to ask questions!

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Living with Cushing's syndrome

Impact

Cushing's syndrome, and the fact that it often takes such a long time for it to be accurately diagnosed, has a big impact on both patients and their families and friends. The disorder has a big impact, not only on your physical and mental health but also on your social and family life. But it affects different individuals in different ways and in differing stages of treatment. It is important that you make it clear what the problems are that you are experiencing, and what it is that you need to get your life back on track again. You are not suffering this illness alone. It is inevitable that it will have an effect on your family and friends as well. Ask your questions, and communicate your problems. The nurse-specialist or the endocrine nurse will play an important role throughout this period.

You have already come a long way and you have put a difficult period behind you. Quite often, patients are somewhat relieved when they first find out what is actually wrong with them. After that, they are focused on the preparations for the operation.

This is followed by what is arguably the worst part: reducing your intake of corticosteroids. This period can last for many months and, for some patients, years. It is a difficult time and it is important that you are aware of that. It is well worth considering asking for help to get you through to the next step. The aim of that next step can be summed up in one word: revitalise. Becoming vigorous again, recuperating in body and spirit.

In the following paragraph we will consider a number of issues that can be of more or less importance to you personally. Everyone is different.

- finding a job and/or keeping your **job**
- your **social life**
- the impact of the illness on your **relationships**, intimate relationships and friendships
- personal development
- **physical exercise**

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Quality of life

The NIVEL study (2005) and the associated baseline measurement showed beyond doubt that people continue to experience residual problems from Cushing's syndrome or Cushing's disease even after a successful operation or other treatment. These illnesses have far-reaching effects, both physical and emotional. There are nearly always residual and distressing problems which affect work, relationships or friendships. They change the patient in subtle ways and the illnesses are sometimes too complex to really understand. To encourage a patient to 'get a grip' is to belittle the suffering. Many people lose their jobs or their relationships hit the rocks. Unfortunately, it is not always possible to avoid the consequences. Disappointment is a bitter pill to have to swallow.

Work

The signs and symptoms that result from Cushing's syndrome will undoubtedly have an impact on your capacity for work. Many people have found that it was simply impossible for them to keep on doing the same job. They can be helped to find other work, or they might find themselves having to rely on incapacity benefit if any work at all has become too strenuous or impossible.

Being able to work is important for everyone. Having a job means:

- having an income and economic independence
- personal growth and development
- social contacts
- structure to the day, having a reason to get up in the morning
- feeling useful, making a difference
- social status
- a better quality of life.



Patient and Partner Education Programme for pituitary/adrenal disorders.

As a result of the disorder, patients can be confronted with changes in their daily lives. The aim of the Patient and Partner Education Programme (PPEP) for people with a pituitary or adrenal disorder is to provide patients and their partners with support in the psychological and social domain. PPEP Pituitary/Adrenal is a self-management programme that consists of eight weekly group meetings. Further information can be found here: [PPEP Pituitary/Adrenal](#).

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During your appointments at the out-patients clinic, your endocrinologist will take note of any limitations you are experiencing. Under certain conditions, information can be exchanged with your company doctor so that he can make himself familiar with the impact of Cushing's syndrome. But you have to give your express permission for this exchange in advance.

Your social life

You will not be an exception if you find you have to stop working, doing voluntary work, taking part in some club and/or enjoying a hobby during the long process before the diagnosis is determined and afterwards. You may have had to disappoint people during that time as your body gradually failed you. Many patients with Cushing's syndrome report that they have had to give up a lot of things.

But this does not need to be the case for ever. You will find that you can become more vigorous again (but perhaps not quite back to your previous level) and that it will once more become possible to take up various activities. Whatever they are, these activities are important because they give substance to your life. Ask your endocrinologist or the nurse-specialist for help, advice or feedback so that you can put your energies to good use.

Intimate relationships

It has been a long journey, finding out that you have Cushing's syndrome. A journey that may have taken years to complete, years in which you were far from being yourself.

Cushing's syndrome is, after all, a progressive and debilitating illness that involves a great deal of emotion. For you, and probably for those around you as well.

If you experience any problems in your relationships, do not hesitate to discuss them with your partner and seek professional help. This is not a sign of weakness. But it is only when you acknowledge a problem that you can deal with it.

Personal development - stand up for yourself

Within the patient association, we like to encourage members to become articulate and conscious of their condition. You are welcome to join their ranks. It means that you will be an active participant in your health and healthcare alongside your endocrinologist. After a while you will be the person who knows your body the best; your healthcare professional is the one whose combined knowledge and experience give him insight into what usually works well in the treatment

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of Cushing's syndrome. But you will find yourself confronted with unexpected incidents as time goes by and, as a result of having Cushing, they may affect you in a different way than someone who doesn't. So, remain alert and ensure that you can take the necessary measures or get someone to do that for you.

Physical exercise

Because of the raised cortisol level, you have an increased chance of cardiovascular disorders and diabetes. Such disorders will also have an impact on your long-term health and they can reduce your life expectancy. Physical exercise and keeping at a healthy weight are important factors in keeping these disorders at bay. Ask your endocrinologist or the nurse-specialist to help you find ways to include more physical exercise in your daily life. Discuss the possibility of a referral to a dietician. It will be worth the effort.



In two minidocumentary's entitled 'Cushing's syndrome', a Cushing patient speaks about the pre-diagnosis period, the tests, the treatment and what it's like living with Cushing's syndrome.

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Do you want to know more about Cushing's syndrome?

Your healthcare professional can put you in touch with patient associations that you could join, so that you can have access to and benefit from the experience and information of other patients.

In the Netherlands, there are two patient associations:

- Dutch Adrenal Society NVACP
- Dutch Pituitary Society

Membership of a patient association brings a lot of benefits. Membership is a serious option for you to consider. In addition, the patient organisations in the Netherlands also promote the interests of their members by entering into discussions about the care to be provided and the availability and supply of medicines. They also provide reliable information about the various clinical aspects of the disorders. They also organise meetings for patients to meet each other and/or learn about the latest developments.

Some Dutch healthcare insurers will pay part of all of the membership fee.

- www.bijniernet.nl
- www.bijniervereniging-nvacp.nl
- www.hypofyse.nl
- www.adrenals.eu

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If you would like a printed copy, you can order one via the webshop of the Dutch Adrenal Society NVACP (www.bijniervereniging-nvacp.nl).

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The contents of this brochure (Dutch and English versions alike) have been compiled with the greatest possible care. Despite this, they might contain errors. We request that you submit any additions or corrections to info@bijniernet.nl

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