CONDITION

Ectopic Cushing syndrome

Ectopic Cushing syndrome is excess cortisol caused by ACTH made by a tumor outside the pituitary gland.

WHAT IT IS
Excess cortisol driven by ACTH from a non-pituitary tumor

BODY SYSTEM
Hormone system and multiple organs

MAIN SYMPTOMS
Muscle weakness, weight gain, high blood pressure, mood changes

WHAT CAUSES IT
ACTH released by a tumor outside the pituitary

HOW IT IS DIAGNOSED
Cortisol and ACTH tests, imaging, sometimes petrosal sinus sampling

MAIN TREATMENT
Tumor treatment and medicines that lower cortisol

CAN IT BE CURED?
Sometimes - when the source tumor can be completely removed

IS IT AN EMERGENCY?
Sometimes - confusion, fainting, or severe breathing difficulty

LONG-TERM OUTLOOK
Often improves when cortisol and the tumor are controlled

Overview

Ectopic Cushing syndrome occurs when a tumor outside the pituitary gland releases adrenocorticotropic hormone, or ACTH, causing the body to make too much cortisol. "Ectopic" means occurring in an unusual place.

ACTH normally comes from the pituitary, a small gland at the base of the brain. It tells the adrenal glands above the kidneys to make cortisol. In ectopic Cushing syndrome, tumor cells make ACTH instead. Less commonly, they release another hormone that stimulates ACTH production.

Cortisol helps regulate blood pressure, blood sugar, inflammation, and the response to stress. High levels over time can weaken muscles and bones, alter mood, increase infection risk, and affect the heart and circulation.

Ectopic Cushing syndrome differs from Cushing disease, which is caused by an ACTH-producing pituitary tumor. Both are forms of Cushing syndrome.

Symptoms may develop quickly when an aggressive tumor produces large amounts of ACTH. Slower-growing tumors may cause gradual changes. Treatment must address both the cortisol excess and the tumor producing ACTH.

Symptoms

Symptoms depend on how high cortisol is and how quickly it rises. They may overlap with symptoms from the underlying tumor.

Common changes include:

Low blood potassium is particularly common. It may cause cramps, constipation, marked weakness, or an abnormal heartbeat.

Some people develop darker skin over scars, knuckles, or skin folds when ACTH is very high. When cortisol rises rapidly, familiar Cushing body-shape changes may be less noticeable than severe weakness, infection, high blood sugar, or low potassium.

- Weakness, especially when climbing stairs or rising from a chair
- High blood pressure or worsening hypertension
- High blood sugar or newly diagnosed diabetes
- Weight gain, often around the abdomen and upper body
- Easy bruising and thin, fragile skin
- Wide purple or reddish stretch marks
- A rounder face or increased fat around the neck
- Anxiety, depression, irritability, or poor sleep
- Bone loss, back pain, or fractures after minor injury
- Frequent or unusually severe infections
- Irregular or absent periods, reduced sex drive, or erectile problems

Causes and risk factors

The cause is usually a neuroendocrine tumor, which begins in cells able to release hormones into the blood.

Associated tumors include small-cell lung cancer and neuroendocrine tumors of the lung, thymus, pancreas, or other organs. Medullary thyroid cancer and several uncommon tumors can also produce ACTH.

Some tumors are cancerous and can spread; others remain small and grow slowly. The amount of ACTH produced does not reliably indicate how aggressive a tumor is.

Smoking increases the risk of small-cell lung cancer, an important cause of ectopic Cushing syndrome. However, many people have another tumor type and no preventable risk factor.

Rare inherited syndromes increase the likelihood of certain neuroendocrine tumors, but most cases are not directly inherited.

Diagnosis

Diagnosis usually happens in stages. Testing first confirms that cortisol is genuinely too high. A random blood cortisol result is generally insufficient because cortisol changes during the day and rises during illness or stress.

Initial tests may include late-night saliva samples, 24-hour urine collections, or a dexamethasone suppression test. Dexamethasone is a steroid medicine that should normally reduce cortisol production. More than one test may be needed.

Once cortisol excess is confirmed, an ACTH blood test helps identify its source. Low ACTH suggests an adrenal cause. Normal or high ACTH suggests either a pituitary tumor or ectopic ACTH production.

Further tests may include:

Inferior petrosal sinus sampling compares blood from veins near the pituitary with blood from elsewhere in the body. This invasive specialist procedure can distinguish a pituitary source from an ectopic source when other findings are unclear.

Very small tumors may not appear on initial scans. Cortisol can still be treated while imaging is repeated over time.

- MRI of the pituitary
- CT or MRI scans of the chest, abdomen, or pelvis
- Hormone stimulation or suppression tests
- Specialized scans that detect neuroendocrine tumor cells
- Inferior petrosal sinus sampling in selected cases

Treatment and management

Treatment aims to control excess cortisol and treat the ACTH-producing tumor.

Surgical removal may provide a cure if the tumor is found and can be removed completely. If surgery is not possible, tumor treatment may include chemotherapy, radiotherapy, targeted medicines, or treatments designed for neuroendocrine tumors. The choice depends on the tumor's type, location, spread, and biological features.

Medicines may reduce cortisol while the tumor is investigated or treated. Metyrapone, osilodrostat, ketoconazole, levoketoconazole, and mitotane interfere with cortisol production. Mifepristone blocks some effects of cortisol rather than lowering its measured level. Intravenous etomidate may be used in hospital for severe cases.

These medicines require monitoring because they can affect liver function, potassium, other hormones, and medication interactions. Lowering cortisol too far can cause adrenal insufficiency.

If severe cortisol excess cannot otherwise be controlled, both adrenal glands may be removed. This stops cortisol production but does not treat the ACTH-producing tumor. Lifelong adrenal hormone replacement is then required.

After successful tumor surgery, the adrenal glands may remain temporarily suppressed. Steroid like prednisone or hydrocortisone replacement may be needed for months or longer while normal cortisol production recovers. Doses are adjusted using symptoms and laboratory tests.

Management may also address high blood pressure, diabetes, low potassium, infection, blood clots, or bone loss.

Complications

Uncontrolled cortisol excess can cause serious infection, diabetes, osteoporosis, fractures, kidney stones, and loss of muscle strength. High blood pressure and unhealthy blood fat levels increase cardiovascular risk.

Cushing syndrome also raises the risk of blood clots, including deep vein thrombosis and pulmonary embolism. Mood disorders, sleep problems, memory difficulties, and occasionally severe confusion or psychosis may occur.

Very low potassium can disrupt heart rhythm. Severe cortisol excess can also make infection harder to recognize by reducing inflammation and fever.

The underlying tumor may cause additional complications depending on its location, growth rate, and whether it has spread.

Prevention

Most cases cannot be prevented, and there is no routine screening test for people without symptoms or a known tumor risk.

Not smoking reduces the risk of small-cell lung cancer but cannot prevent neuroendocrine tumors from other causes. Stopping smoking may improve overall health and the ability to tolerate cancer treatment.

People with an inherited tumor syndrome may receive condition-specific monitoring to help find certain tumors earlier.

Living with it and what to expect

The outlook depends on both cortisol control and the behavior of the underlying tumor.

Blood pressure, blood sugar, mood, bruising, and infection risk may improve within weeks or months after effective treatment. Muscle strength and bone density often recover more slowly, and some effects may not resolve completely.

Recovery can be uneven. After cortisol falls, some people experience tiredness, aching, low mood, or reduced stamina even while receiving appropriate replacement steroids. The body may need time to adjust after prolonged exposure to high cortisol.

Even after complete tumor removal, follow-up is needed to check for recurrent cortisol excess or tumor growth. If the source was not found, repeat scans may eventually reveal a previously hidden, slow-growing tumor.

When a tumor cannot be removed, medicines may control cortisol for an extended period. Treatment may change if side effects develop, cortisol rises again, or the tumor changes.

Follow-up commonly includes hormone tests, imaging, blood pressure and blood sugar checks, potassium monitoring, and assessment of bone health. People taking steroid replacement need guidance about missed doses, illness, medical alert identification, and emergency steroid treatment.

When to get medical help

Arrange medical follow-up for gradual changes such as increasing weakness, unexplained bruising, worsening blood pressure or blood sugar, new stretch marks, menstrual changes, or persistent mood symptoms. These symptoms have many possible causes and need proper assessment.

If you have diagnosed ectopic Cushing syndrome, contact your care team promptly for fever, infection symptoms, worsening swelling, new medication side effects, or the clear return of previous cortisol-related symptoms.

Seek urgent medical assessment for:

Call emergency services for severe breathing difficulty, chest pain, coughing up blood, fainting, a seizure, or sudden severe confusion.

After cortisol-lowering treatment or adrenal surgery, severe weakness, vomiting, abdominal pain, fainting, or confusion may indicate an adrenal crisis. This is an emergency caused by dangerously low cortisol and requires immediate treatment.

- New one-sided leg pain or swelling
- Palpitations with marked weakness or muscle cramps
- Persistent vomiting or inability to keep steroid medicine down
- Rapidly worsening confusion, agitation, or unusual behavior

Common questions

Is ectopic Cushing syndrome cancer?

The syndrome is a hormone condition, not cancer. However, it is caused by a tumor that may be cancerous or noncancerous. Some associated tumors grow slowly; others are more aggressive.

What is the difference between Cushing disease and ectopic Cushing syndrome?

Both involve excess ACTH and cortisol. In Cushing disease, ACTH comes from a pituitary tumor. In ectopic Cushing syndrome, it comes from a tumor elsewhere in the body.

Can ectopic Cushing syndrome be cured?

Sometimes. A cure may be possible if the ACTH-producing tumor is found and completely removed. Otherwise, treatment may still control cortisol and treat or slow the tumor.

Will the weight gain and muscle weakness go away?

They often improve once cortisol is controlled, but muscle strength may take many months to rebuild. Age, bone health, duration of cortisol excess, and the underlying tumor affect

recovery.

Why can't doctors find the tumor?

Some ACTH-producing tumors are extremely small or difficult to see on imaging. They may become visible on later scans. Treatment to control cortisol does not always need to wait until the source is found.

Does "ectopic" mean this is related to ectopic pregnancy?

No. "Ectopic" means in an abnormal location. Here, it refers to ACTH being produced outside its usual source, the pituitary gland.

Sources

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