

Cushing's Disease

Cushing's disease is a hormone disorder resulting in many distressing symptoms. At present, surgery, radiotherapy, and medicines are available. Pioneering research continues to help patients lead more normal lives.

What is Cushing's disease?

Cushing's disease is a hormonal disorder caused by prolonged exposure of the body's tissues to high levels of the glucocorticoid steroid hormone cortisol. It is named after Harvey Williams Cushing, an American neurosurgeon who is credited with describing this disease in his work *"The Pituitary Body and its Disorders"* which appeared in 1912. Cortisol helps maintain blood pressure and cardiovascular function, reduces the immune system's inflammatory response, balances the effects of insulin, and regulates the metabolism of proteins, carbohydrates, and fats. Another important function of the hormone is to support the body's response to stress.

The production of cortisol follows a precise chain of events. The hypothalamus, a part of the brain, sends corticotrophin releasing hormone (CRH) to the pituitary gland, which is also situated in the brain. CRH causes the pituitary to secrete the hormone adrenocorticotrophin (ACTH), which stimulates the adrenal glands. When the adrenals, which are named after their location just above the kidneys, receive the ACTH, they release cortisol into the bloodstream. When cortisol levels are adequate, less CRH and ACTH are released. However, if something goes wrong in this hypothalamic-pituitary-adrenal (HPA) cascade, cortisol production can go awry.

Symptoms vary, but most people have upper body obesity, a rounded "moon" face, increased fat around the neck, and thinning arms and legs. Children tend to be obese and show growth retardation. Other symptoms appear in the skin, which becomes fragile and thin. Purplish pink streaks may appear on the abdomen, thighs, buttocks, arms and breasts. The bones are weakened and routine activities may lead to backaches, rib and spinal column fractures.

Most people complain about severe fatigue, weak muscles, high blood pressure and elevated blood sugar. Anxiety and signs of depression are common. Women usually have excess hair growth on their face, chest, abdomen, and thighs. Their menstrual periods may become irregular or stop. Men have decreased fertility, with diminished or absent libido.

Who does Cushing's disease affect?

Cushing's disease is relatively rare and most commonly affects adults aged 20 to 50. An estimated 10 to 15 people per million are affected each year, which corresponds to 4,000 and 6,000 cases a year in Europe. Single pituitary adenomas are responsi-





Harvey Williams Cushing

ble for most cases of Cushing's disease. They are benign tumours of the pituitary gland which secrete increased amounts of ACTH. Cushing's disease affects women five times more frequently than men. It is not hereditary.

Sometimes, an abnormality of the adrenal glands, most often an adrenal tumour, causes Cushing's syndrome, which shows the same clinical signs and symptoms as Cushing's disease.

The average age of onset is about 40 years. Most of these cases involve non-cancerous tumours of adrenal tissue, which release excess cortisol into the blood. Many patients suffer from the symptoms of Cushing's syndrome because they take glucocorticoid medication for their underlying disease: asthma, rheumatoid arthritis, lupus erythematosus and other auto-immune disorders, or for immunosuppression after transplantation.

Present treatments

Unless treated, Cushing's disease is associated with high morbidity and ultimately mortality. The therapeutic goal in the treatment is normalisation of plasma ACTH and serum cortisol values, tumour shrinkage, and preservation of pituitary function.

The most widely used treatment for Cushing's disease is surgical removal of the tumour. So far, no effective medical therapy exists for ACTH-secreting pituitary tumours. After curative pituitary surgery, the production of ACTH temporarily drops to levels below normal. This is a natural mechanism, and patients are given a synthetic form of cortisol such as hydrocortisone or prednisone. Most patients can stop this replacement therapy in less than a year.

For patients in whom surgery has failed or who are not suitable candidates, radiotherapy is another option. It may take several months before patients feel better after radiation treatment alone. The combination of radiation and treatment with cortisol-blocking medicines can speed the recovery. There are several compounds available which suppress cortisol production and lower plasma and urine hormone levels. Treatment with one of the medicines alone or in combination to control synthesis of cortisol can be successful in 30 to 40 per cent of patients.

Current medical therapy for Cushing's disease also includes neuro-modulating compounds that act at the hypothalamic-pituitary level, such as serotonin antagonists, dopamine agonists, gamma-aminobutyric acid (GABA) agonists, and somatostatin receptor binding molecules. While these treatments have all been reported to work, they do not impact on pituitary tumour growth. Thus, current therapy with medicines is largely reserved for pre-operative treatment or in cases where the tumour cannot be located, or whenever a definitive treatment is delayed.

What's in the development pipeline?

Researchers are evaluating the effectiveness and tolerability of a growth hormone analogue in patients with Cushing's disease who are candidates for surgical intervention, as well as patients who have recurrent Cushing's disease post-operatively. Patients will self-administer the new compound via injections twice daily for 15 days. This study is in phase 2 clinical trials.

Scientists are studying the relationship between dysregulation of the HPA cascade and disorders of mood, function during sleep, and cognition in patients with Cushing's disease. They are also trying to identify subgroups of patients who differ in the presence and severity of the depressive syndrome, and to uncover HPA axis dysregulation differences

Another researcher group is investigating the effects of cortisol on brain structure and function. Patients with Cushing's disease are studied before and after treatment. Brain

imaging and neuro-psychological tests are used to study changes in the brain area of the hippocampus and thinking and learning functions as well as mood during the period of elevated cortisol. Since elevated cortisol and dysregulation of its secretory system occurs in a significant proportion of the aged and in major depressive disorder, the study will also help advance knowledge of the role of cortisol in these conditions.

Another approach could be treatment with a new anti-glucocorticoid compound which attaches to glucocorticoid receptors in the body and thus prevents the hormone cortisol from binding. This project is still in a very early preclinical phase.

Since accurate diagnosis is still a problem for some patients, new tests are under study to further refine the diagnostic process.

The longer-term future

It has been found in laboratory experiments that molecules that attach to the peroxisome-proliferator activating receptor-gamma (PPAR) strongly influence ACTH secretion and cell growth. Compounds that bind to PPAR and mediate its actions include the thiazolidinedione (TZD) compounds that are commonly employed in the oral treatment of type 2 diabetes. As researchers could demonstrate that PPAR expression is abundantly found in ACTH secreting tumours surgically removed from patients with Cushing's disease, these findings suggest a potential role for TZD compounds in the management of the condition.

Studies are underway to understand the causes of formation of benign endocrine tumours, such as those which cause most cases of Cushing's syndrome. In a few pituitary adenomas, specific gene defects have been identified and may provide important clues to understanding tumour formation. Endocrine factors may also play a role. There is increasing evidence that tumour formation is a multi-step process. Understanding the basis of Cushing's disease will yield new approaches to therapy.



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