Chapter 6

The Internal Wildlife of Hypercortisolism: Cushing`S Syndrome

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Abstract

Cushing's syndrome can arise from pituitary ACTH, ectopically produced ACTH, an adrenal tumor, or medication. Cushing's disease, which refers to the condition caused by excess pituitary ACTH leading to adrenal gland enlargement, is a complex and challenging endocrine disorder. It should be considered in patients with unusual symptoms for their age, those displaying multiple and worsening features, and those with adrenal incidentalomas. It's also a common issue in children who fail to grow in height percentiles while gaining weight. Endogenous Cushing's syndrome is more prevalent in women. About 80% of cases result from an ACTH-dependent cause, with 80% of those being due to a pituitary adenoma (Cushing's disease) and the remaining 20% due to ectopic ACTH secretion. The other non-ACTH-dependent causes of Cushing's syndrome stem from benign adrenal adenomas (60%) and carcinomas biochemically (40%). Given the specialized nature of the treatment, all cases need to be referred to a major medical center. The most distinctive clinical signs for

diagnosing endogenous Cushing's syndrome include thin skin, easy bruising, and muscle weakness. There should be a strong clinical suspicion before starting investigations. The diagnosis relies on a combination of dexamethasone suppression tests, loss of circadian rhythm, and urine tests for free cortisol. However, differentiating pituitary from non-pituitary sources of excess ACTH should ideally use mical tests. Treatment for endogenous Cushing's syndrome involves using drugs to reduce corticosteroid levels before surgery or in cases where tumors cannot be surgically removed. The preferred surgical approach for Cushing's disease is transsphenoidal surgery; in cases of recurrence or tumors that can't be reset, bilateral laparoscopic adrenalectomy can be considered.

Keywords: Cushing's syndrome, Exogenous Cushing's syndrome, Endogenous Cushing's syndrome, Excess of glucocorticoids, ACTH.

1. Introduction

1.1 Definition

Cushing syndrome is a chronic and systemic clinical condition on the prolonged action of an increase in plasma cortisol levels, ranging from 2 to 8 million people annually. It is not due to a physiological etiology, but due to the most frequent cause of exogenous steroid usage [1]. It is also associated with hyperglycemia, protein catabolism, immunosuppression, hypertension, weight gain, neurocognitive changes, and mood disorders. Cushing's syndrome is an ongoing clinical challenge [1][2].

1.2 Historical context

In 1912, Cushing’s syndrome was formally identified by the American neurosurgeon Dr. Harvey Cushing, and it was based on his patient

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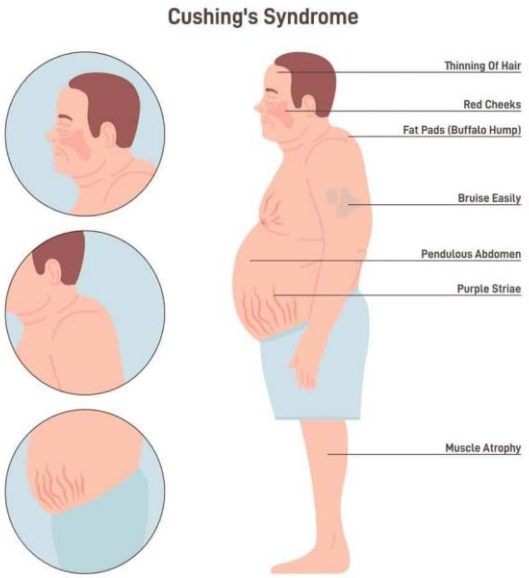
Minnie G [2][3]. Initially, it was described as a “polyglandular” disorder involving the pituitary basophilism. Later, it was understood to be the overproduction of ACTH-dependent [pituitary] or independent [adrenal] cortisol, with major advances in diagnosis and treatment emerging throughout the 20th century.[3]

1.3 Epidemiology

Cushing`s syndrome is identified as a rare, severe endocrine disorder with an annual disease record of 1.8-4.5 cases per million people. It primarily affects 30-50-year-old adults, with a 3:1 to 4:1 female predominance.[4]



2. Etiology and pathophysiology

2.1. Exogenous Cushing’s syndrome

Exogenous Cushing syndrome is a form of Cushing`s syndrome that occurs in people taking glucocorticoid (also called corticosteroid, or steroid) hormones. Exogenous Cushing syndrome occurs when a person takes man-made (synthetic) glucocorticoid medicines to treat a disease. These medicines act like cortisol in the body. Prednisone,

dexamethasone, and prednisolone are examples of this type of medicine.

2.2. Endogenous Cushing`s syndrome

A rare group of endocrine disorders caused by prolonged and high exposure levels to glucocorticoids of endogenous (adrenal cortex production) origin. Typical clinical features are truncal and facial obesity, hypercatabolic syndrome (thinned skin, purple striae, ecchymosis, bruising with no obvious trauma, proximal muscle weakness with amyotrophy, osteoporosis), and, in children, weight gain with decreasing growth velocity.

2.3 Cushing`s disease

Cushing's disease is caused by a tumor or excess growth (hyperplasia) of the pituitary gland. The pituitary gland is located just below the base of the brain. A type of pituitary tumor called an adenoma is the most common cause. An adenoma is a benign tumor (not a cancer).

With Cushing's disease, the pituitary gland releases too much ACTH. ACTH stimulates the production and release of cortisol, a stress hormone. Too much ACTH causes the adrenal glands to make too much cortisol.

3. Clinical Manifestations

The syndrome presents with many characteristic physical characteristics, metabolic disturbances, neuro-psychiatric symptoms, and reproductive abnormalities.

3.1 *Physical features*

Patients with the syndrome usually exhibit central obesity with thin arms and legs, a round moon face, and a fat hump between the shoulders [buffalo hump]. Pink and purple striae are commonly seen

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on the abdomen, thighs, breasts, and underarms. regions. The skin becomes thin, fragile, and bruises easily, with a slow wound-healing process. Other physical features include acne and hirsutism [excess facial and body hair in women], and temporal balding in females, also in males, who have symptoms like reduced fertility and erectile dysfunction

3.2 *Metabolic and cardiovascular effects*

Excess cortisol can lead to hypertension, glucose intolerance, and type 2 diabetes. Patients may also develop osteoporosis, muscle wasting, and weakness, particularly in the proximal muscles of the limbs. Renal calculi and increased susceptibility to infections are additional complications.

3.3 *Neuropsychiatric symptoms*

Cushing syndrome can cause depression, anxiety, irritability, and emotional instability. Cognitive effects include trouble concentrating, memory impairment, and Insomnia. Severe cases may present with psychosis or extreme fatigue.

4. Diagnostic evaluation and algorithm

Screening tests are essential for identifying underlying, treatable causes in patients such as young - onset hypertension (<30 – 40 years) or secondary osteoporosis.

4.1. *Initial screening/ algorithm*

{a} BP measurement

It is done with the help of a 24-hour BP monitor, a device that is used to check your blood pressure automatically throughout the day and night.

{b} Initial labs

Every patient goes through these tests to check their health condition. For kidney functioning, a urine test and a blood test were taken. For the salt level, to check minerals like potassium in your blood, blood sugar, and cholesterol tests were taken for diabetes and heart health, and finally, a thyroid test to check whether the thyroid gland is working properly.

{c} Initial screening

A bone density scan that checks the strength of the bones in the hip and spine, a blood test to check vitamin D and calcium levels in the blood, and hormone issues that might be weakening your bones. A 24-hour urinary free cortisol (UFC) test is conducted to measure the total amount of active cortisol released into urine over 24 hours to diagnose Cushing syndrome and adrenal disorders. I mg overnight dexamethasone suppression test (DST), a common screening tool to determine if the body is producing excess cortisol, a condition known as Cushing's syndrome. If a person takes synthetic steroids like dexamethasone, the pituitary gland stops releasing ACTH hormone, which in turn, the adrenal glands stop making cortisol.

5. Treatment and management

Management of Hypercortisolism Syndrome is primarily managed along the lines of Cushing's disease. The goal of management is to reduce plasma cortisol to normal to minimize the potential for complications from hypercortisolism, such as osteoporosis, hypertension, and type 2 diabetes. Endogenous hypercortisolism due to an ACTH-secreting tumor is treated with surgical removal of the tumor. The initial management for Cushing's disease and for an adrenal cortical tumor is surgery. Specifically, the primary

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management of Cushing's disease is with transsphenoidal surgery, and of an adrenal cortical tumor is adrenalectomy.

In the event of surgical failure (because of ectopic ACTH or metastatic adrenal carcinoma) and considering the frequency of drug failure, one can also try to control hypercortisolism medically in the context of Cushing syndrome. In the context of ACTH-dependent disease, adrenalectomy is a possible subsequent option. Pituitary radiation may also be an option in the case of recurrence of Cushing's disease after initial successful surgery.

In 2015, the Endocrine Society released the new guidelines for Cushing syndrome:

Cushing syndrome treatment: The treatment of choice is surgical removal of the adenoma causing the syndrome, excluding situations where steroid levels are not expected to decrease or when surgery is contraindicated. Second-line treatment should be planned on a case-by-case basis.

Alternative first-line treatments include surgical resection of ectopic ACTH-secreting tumors; transsphenoidal selective adenectomy; blocking hormone receptors in cases of bilateral micronodular adrenal hyperplasia; and surgical removal in cases of bilateral adrenal tumors.

5.1. *Normalization of cortisol or glucocorticoid activity*

It also includes the normalization of comorbid conditions (such as blood pressure or blood sugar) by additional drugs (such as antihypertensive drugs). Lowering blood glucose or blood pressure in a state of hyperglycemia or hypertension induced by excess cortisol decreases insulin resistance, lipid metabolism abnormalities, and obesity. Although adrenalectomy is a definitive therapy for the great

majority of children and adults suffering from benign unilateral adrenal adenoma, the management of unilateral adrenal carcinomas remains a challenge because of a relatively poor overall prognosis. In this context, surgical removal of the carcinoma is recommended with possible adjunctive therapy with steroid inhibitors to control cortisol hyperproduction.

6. Conclusion

Cushing syndrome is a multi-system disease requiring a coordinated approach for prompt diagnosis and treatment to avert high mortality, improve quality of life, and solve problems. Endogenous Cushing's syndrome is a common endocrine disorder caused by chronic glucocorticoid excess. This leads to multiple clinical features, secondary complications, and an increased mortality rate despite treatment. Many of the molecular features and genetic alterations underlying the various causes of Cushing's syndrome have been uncovered over the last decade. The techniques of imaging and biochemical assessment have evolved. The management of Cushing's syndrome is still, however, challenging. Surgery is the first line of treatment for all causes, but medical treatment is becoming increasingly effective with the emergence of new drugs for use in hypercortisolism. Other chronic sequelae and complications, however, remain and can still significantly impact the quality of life of patients who achieve clinical remission. Therefore, accurate and prompt diagnosis and treatment of Cushing's syndrome are important to avert long-term effects of chronic glucocorticoid excess and improve patient survival and well-being. This chapter aims to review and update the management of endogenous Cushing's syndrome of all aetiologies.

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