Primary Hypercortisolism

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KEYWORDS

• Adrenal tumor • Cushing's syndrome • Cortisol overproduction • Endogenous hypercortisolism • Adrenal hyperplasia • Glucocorticoid excess

KEY POINTS

- Primary hypercortisolism, also known as ACTH (adrenocorticotropic hormone)-independent Cushing's syndrome, is characterized by excessive cortisol production due to a direct issue with the adrenal glands, often caused by an adrenal tumor or adrenal hyperplasia.
- Unlike secondary hypercortisolism, this condition is not driven by excess ACTH from the pituitary gland.
- Common symptoms include weight gain, high blood pressure, skin changes, muscle weakness, and glucose intolerance.
- Diagnosis is made through cortisol level testing, imaging studies (CT/MRI), and differentiating it from ACTH-dependent causes.
- Treatment typically involves surgical removal of the adrenal tumor, followed by hormone replacement therapy if necessary.

INTRODUCTION

Primary hypercortisolism, also known as ACTH (adrenocorticotropic hormone)-independent Cushing's syndrome, is a rare endocrine disorder characterized by excessive and autonomous cortisol production by the adrenal glands.[1]

Cortisol, a vital glucocorticoid hormone, is essential for maintaining homeostasis, particularly in the body's response to stress, metabolism, immune function, and inflammation regulation. The overproduction of cortisol disrupts these physiologic processes, leading to a constellation of clinical features that can significantly impact the patient's quality of life and increase morbidity and mortality.

The term *Cushing's syndrome* encompasses a spectrum of disorders characterized by chronic hypercortisolism, regardless of the underlying cause. Primary hypercortisolism specifically refers to cases where the source of excess cortisol lies within the adrenal glands themselves, independent of external stimulation by ACTH. This contrasts with the more common ACTH-dependent Cushing's syndrome, where elevated ACTH levels drive excessive cortisol production, typically due to a pituitary adenoma (Cushing's disease) or ectopic ACTH production from nonpituitary tumors.

The recognition of primary hypercortisolism as a distinct clinical entity dates back to the early 20th century, following Harvey Cushing's seminal work in identifying the symptoms and underlying causes of Cushing's syndrome. However, it was not until later that the differentiation between ACTH-dependent and ACTH-independent forms was clearly established, leading to more accurate diagnosis and targeted treatment strategies.

Despite being less common than ACTH-dependent Cushing's syndrome, primary hypercortisolism is of particular clinical interest due to its diverse etiologies, ranging from benign adrenal adenomas to aggressive adrenal carcinomas, and

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Abbreviations

ACC	adrenocortical carcinomas
ACTH	adrenocorticotropic hormone
CT	computed tomography
HDDST	high-dose dexamethasone suppression test
LDDST	low-dose dexamethasone suppression test
LNSC	late-night salivary cortisol
MAS	McCune-Albright syndrome
PBMAH	primary bilateral macronodular adrenal hyperplasia
PPNAD	primary pigmented nodular adrenal disease
UFC	urinary free cortisol

rare genetic conditions such as primary pigmented nodular adrenal disease (PPNAD) and primary bilateral macronodular adrenal hyperplasia (PBMAH).

The pathophysiology of primary hypercortisolism is rooted in the dysregulation of cortisol synthesis within the adrenal cortex. Normally, cortisol production is tightly regulated by the hypothalamic-pituitary-adrenal axis through a negative feedback loop involving corticotropin-releasing hormone, ACTH, and cortisol itself. In primary hypercortisolism, this regulatory loop is disrupted, leading to unrestrained cortisol secretion. This autonomous cortisol production not only suppresses ACTH release but also results in a range of metabolic, cardiovascular, and neuropsychiatric disturbances.

Clinically, primary hypercortisolism manifests with a spectrum of symptoms that overlap with other forms of Cushing's syndrome, including central obesity, facial rounding (moon face), muscle weakness, hypertension, glucose intolerance, osteoporosis, and psychiatric disorders. However, distinguishing primary hypercortisolism from its ACTH-dependent counterparts is crucial, as the management strategies differ significantly. For example, while ACTH-dependent Cushing's syndrome may require treatment directed at the pituitary or ectopic source of ACTH, primary hypercortisolism is typically managed with surgical resection of the adrenal lesion.

In addition to the challenges in diagnosis and treatment, primary hypercortisolism is associated with considerable long-term morbidity, even after successful treatment. The chronic exposure to high cortisol levels can have lasting effects on cardiovascular health, bone density, and mental well-being, necessitating ongoing monitoring and management of these patients. Moreover, the risk of recurrence, particularly in cases of adrenal carcinoma, underscores the need for vigilant follow-up and the potential for adjuvant therapies.

Given the rarity and complexity of primary hypercortisolism, it remains a subject of ongoing research and clinical interest. This document aims to provide a comprehensive overview of the current knowledge on primary hypercortisolism, encompassing its pathophysiology, clinical presentation, diagnostic strategies, and treatment options. By synthesizing the latest scientific literature and clinical guidelines, this review seeks to equip health care professionals with the information necessary to effectively diagnose, treat, and manage patients with primary hypercortisolism, ultimately improving patient outcomes and advancing the field of endocrinology.

ETIOLOGY/PATHOGENESIS

Primary hypercortisolism, also known as ACTH-independent Cushing's syndrome, arises from intrinsic abnormalities within the adrenal glands, leading to excessive cortisol production independent of ACTH regulation.[2] This condition contrasts with ACTH-dependent Cushing's syndrome, where cortisol excess is driven by elevated ACTH levels from the pituitary gland or an ectopic source. The etiology of primary hypercortisolism is diverse, encompassing a range of benign and malignant adrenal pathologies, as well as genetic syndromes and rare conditions.

Adrenal Adenomas

Adrenal adenomas are benign tumors of the adrenal cortex and represent the most common cause of primary hypercortisolism. These adenomas are usually unilateral, although bilateral adenomas can occur. The autonomous secretion of cortisol by these tumors leads to the suppression of ACTH secretion from the pituitary gland, resulting in reduced stimulation of the contralateral adrenal gland, which often becomes atrophic. Adrenal adenomas typically present with the classical features of Cushing's syndrome, including central obesity, hypertension, glucose intolerance, and skin changes. The clinical course is often indolent, with symptoms developing gradually over months or years. Surgical resection of the adenoma is the primary treatment and often leads to the resolution of hypercortisolism.

Adrenocortical Carcinomas

Adrenocortical carcinomas (ACCs) are rare, aggressive malignant tumors of the adrenal cortex that can produce excessive amounts of cortisol. Unlike benign adenomas, ACCs may also secrete other adrenal steroids, including androgens, estrogens, and mineralocorticoids, leading to a mixed

clinical presentation. The excessive cortisol production by the tumor suppresses ACTH secretion, causing atrophy of the contralateral adrenal gland. ACCs are associated with a poor prognosis due to their aggressive nature and high potential for metastasis. Patients may present with a rapidly progressing form of Cushing's syndrome, often with additional symptoms related to excess androgen or estrogen production. Treatment typically involves surgical resection, often followed by adjuvant therapies such as mitotane or chemotherapy, although the overall survival rates remain low.

Primary Bilateral Macronodular Adrenal Hyperplasia

PBMAH is a rare cause of primary hypercortisolism characterized by the presence of multiple large nodules in both adrenal glands. Unlike adenomas or carcinomas, PBMAH involves hyperplasia (increased number of cells) rather than a discrete tumor. The hyperplastic adrenal tissue autonomously secretes cortisol, leading to ACTH suppression and further adrenal hyperplasia. PBMAH typically presents in middle-aged or older adults with a milder form of Cushing's syndrome, often detected incidentally. The clinical course can be variable, with some patients developing significant hypercortisolism over time. Management options include bilateral adrenalectomy in severe cases or medical therapy to control cortisol production.

Primary Pigmented Nodular Adrenocortical Disease

PPNAD is a rare form of primary hypercortisolism, often associated with Carney complex, a genetic syndrome characterized by multiple neoplasms and skin lesions. PPNAD is characterized by the presence of multiple small, pigmented nodules in the adrenal cortex. These nodules autonomously produce cortisol, leading to ACTH-independent Cushing's syndrome. PPNAD typically presents with Cushing's syndrome in adolescence or early adulthood. The syndrome can be cyclical, with periods of hypercortisolism interspersed with normal cortisol levels. Treatment usually involves bilateral adrenalectomy, as the hypercortisolism is due to diffuse disease rather than a single lesion.

McCune-Albright Syndrome

McCune-Albright syndrome (MAS) is a rare genetic disorder caused by postzygotic activating mutations in the guanine nucleotide-binding protein, alpha stimulating (GNAS) gene, leading to mosaicism. MAS is characterized by the triad of fibrous dysplasia of bone, café-au-lait skin spots, and endocrine abnormalities, including hypercortisolism due to adrenal hyperplasia. Cushing's syndrome in MAS is typically seen in infancy or early childhood and may present with severe symptoms, including growth retardation, failure to thrive, and developmental delays. The management of hypercortisolism in MAS is challenging and may involve a combination of medical therapy and surgical intervention.

Ectopic Adrenocorticotropic Hormone Production

While primary hypercortisolism is classically ACTH-independent, there are rare cases where ectopic ACTH production can lead to adrenal hyperplasia and subsequent cortisol excess. This ectopic ACTH production can occur in tumors outside the pituitary gland, such as small cell lung cancer or carcinoid tumors. Ectopic ACTH production can lead to rapid and severe hypercortisolism, with prominent features such as severe muscle weakness, hyperglycemia, and hypertension. The treatment involves addressing the underlying tumor, either through surgical resection, radiation, or chemotherapy, depending on the tumor type and stage.

Iatrogenic Causes and Paraneoplastic Syndromes

- Iatrogenic Cushing's syndrome: Though not a form of primary hypercortisolism, iatrogenic Cushing's syndrome is a critical consideration in differential diagnosis. It results from the exogenous administration of glucocorticoids, leading to clinical features indistinguishable from endogenous hypercortisolism. This form is common due to the widespread use of steroids in treating various inflammatory and autoimmune conditions.
- Paraneoplastic syndromes: Certain tumors, though not directly causing adrenal hyperplasia or adenomas, may lead to paraneoplastic syndromes where cortisol levels are elevated indirectly, often involving complex interactions between tumor-secreted factors and adrenal function.

Cyclical Cushing's Syndrome

Cyclical Cushing's syndrome is characterized by intermittent episodes of hypercortisolism interspersed with periods of normal cortisol secretion. This phenomenon can occur in both primary and secondary forms of hypercortisolism and adds a layer of complexity to the diagnosis and management. Cyclical Cushing's syndrome can present diagnostic challenges due to the fluctuating nature of cortisol levels, leading to periods where clinical

features may partially or fully resolve. Repeated testing over time is often necessary to capture the hypercortisolism phase and confirm the diagnosis.

EPIDEMIOLOGY

Prevalence and Incidence

The overall prevalence of endogenous Cushing's syndrome, including both ACTH-dependent and ACTH-independent forms, is estimated to be approximately 1 to 2 cases per million people per year. Primary hypercortisolism represents a subset of these cases, with estimates suggesting that ACTH-independent Cushing's syndrome accounts for about 20% to 30% of all cases of endogenous Cushing's syndrome.[2]

Due to its rarity, primary hypercortisolism is often underdiagnosed or misdiagnosed, especially in milder cases or those with atypical presentations. The prevalence of adrenal incidentalomas (adrenal tumors discovered incidentally on imaging studies) has increased with the widespread use of imaging techniques. Studies have shown that up to 10% of individuals with adrenal incidentalomas may have subclinical Cushing's syndrome,[3] where cortisol production is mildly elevated without overt clinical symptoms. This condition is more common in older adults and may contribute to the overall burden of hypercortisolism in the population.

With respect to incidence of primary hypercortisolism, it may vary depending on the underlying etiology. For instance, adrenal adenomas, the most common cause of primary hypercortisolism, have an incidence of approximately 0.6 cases per million per year. These adenomas are usually unilateral and are often detected incidentally during imaging for unrelated conditions. On the contrary, adrenal carcinomas are rare, with an estimated incidence of 0.5 to 2 cases per million people per year. Although rare, these tumors are aggressive and account for a significant proportion of cases of primary hypercortisolism. The incidence of PBMAH is difficult to ascertain due to its rarity and the fact that it often presents with subclinical or mild hypercortisolism.[4] Estimates suggest an incidence of less than 1 case per million people per year. Finally, PPNAD is an extremely rare cause of primary hypercortisolism, typically associated with genetic conditions like Carney complex.[5] The incidence of PPNAD is not well-established but is thought to be much less than 1 case per million per year.

Demographic Distribution

Primary hypercortisolism can occur at any age, but the age of onset varies depending on the underlying cause. Adrenal adenomas are more common in middle-aged and older adults, typically presenting between the ages of 40 and 60 years, whereas adrenal carcinomas can occur at any age but have a bimodal distribution, with peaks in early childhood and middle adulthood. PBMAH is often diagnosed in adults, typically presenting in the fourth or fifth decade of life; PPNAD often presents in adolescence or early adulthood, particularly in patients with Carney complex.

With respect to gender, there is a disparity in the prevalence of primary hypercortisolism, which varies by etiology.[6] Adrenal carcinomas do not show a significant gender predilection, with a near-equal incidence in males and females. By contrast, adrenal adenomas are more common in women, with a female-to-male ratio of approximately 3:1. The reason for this gender difference is not fully understood but may relate to differences in adrenal gland biology and hormonal regulation. Both PBMAH and PPNAD tend to affect women more frequently, though the exact female-to-male ratio varies across studies.

Genetic Syndromes

Several genetic syndromes are associated with an increased risk of developing primary hypercortisolism.[7] Carney Complex is an autosomal dominant disorder characterized by multiple neoplasms, including PPNAD, myxomas, and skin pigmentation. Mutations in the protein kinase, cAMP-dependent, regulatory, type I, alpha (PRKAR1A) gene are a common cause of Carney complex and PPNAD. Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) brings higher risk of developing adrenal tumors, including adrenocortical carcinoma, which can lead to primary hypercortisolism. Li-Fraumeni Syndrome, a syndrome caused by mutations in the TP53 gene, predisposes individuals to a variety of cancers, including adrenal carcinoma, which can cause primary hypercortisolism. Finally, Multiple Endocrine Neoplasia Type 1, though more commonly associated with pituitary, parathyroid, and pancreatic tumors, can occasionally be associated with adrenal tumors that lead to primary hypercortisolism.

Environmental and Lifestyle Factors

While genetic factors play a significant role, environmental and lifestyle factors may also influence the development of primary hypercortisolism. There is a higher prevalence of adrenal incidentalomas in obese individuals, some of which may secrete cortisol autonomously, leading to subclinical or overt Cushing's syndrome. Hypertension and Type 2 Diabetes are commonly associated with metabolic syndrome and may increase the likelihood of identifying adrenal adenomas or other

adrenal pathologies during medical evaluation. Although not a cause of primary hypercortisolism, the use of exogenous glucocorticoids can complicate the diagnosis by mimicking some features of the syndrome, and careful differentiation is needed.

CLINICAL PRESENTATION

The signs and symptoms can vary widely depending on the severity and duration of hypercortisolism, the underlying cause, and individual patient factors such as age, gender, and comorbid conditions.[8] The clinical presentation is often insidious, with symptoms gradually worsening over time,[9] making early diagnosis challenging.

General Features

One of the most common and noticeable symptoms of primary hypercortisolism is progressive weight gain, particularly in the trunk or central body. This central obesity often contrasts with relatively thinner limbs, a phenomenon sometimes described as *buffalo hump* when fat accumulates on the upper back.

Patients often develop characteristic facial changes, including facial rounding (moon face), facial plethora (redness), and a ruddy complexion. These changes are due to increased fat deposition and changes in skin vasculature.

Hypercortisolism can also cause several notable skin changes, such as: *skin atrophy*, with the skin thin and fragile, making it prone to bruising and tears even with minor trauma, and *purple striae*, wide, reddish-purple stretch marks, particularly on the abdomen, thighs, breasts, and arms, are highly suggestive of hypercortisolism. These striae result from the breakdown of skin collagen due to prolonged exposure to high cortisol levels. Although more common in ACTH-dependent Cushing's syndrome, some patients with primary hypercortisolism may also develop hyperpigmentation, particularly in areas of friction or scars. Cortisol can cause increased androgen production, leading to acne and excessive hair growth (hirsutism) in women, particularly on the face, chest, and back.

Finally, muscle weakness, particularly in the proximal muscles of the arms and legs, is a common feature of primary hypercortisolism. Patients may report difficulty climbing stairs, rising from a chair, or lifting objects. This weakness is due to muscle atrophy and wasting caused by the catabolic effects of cortisol on protein metabolism.

Metabolic and Cardiovascular Manifestations

Hypertension is a hallmark of primary hypercortisolism and is present in the majority of patients.[10] Cortisol increases blood pressure by enhancing the sensitivity of blood vessels to catecholamines and increasing sodium retention, leading to volume expansion. This hypertension is often resistant to standard antihypertensive treatments, necessitating specific therapies targeting the underlying hypercortisolism.

Cortisol has a profound impact on glucose metabolism, leading to insulin resistance, hyperglycemia, and, in some cases, overt type 2 diabetes mellitus.[11,12] Patients may present with symptoms of hyperglycemia such as increased thirst, frequent urination, and unexplained weight loss, although weight loss is less common in those with significant central obesity.

Patients with primary hypercortisolism often exhibit dyslipidemia, characterized by elevated levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, along with low levels of high-density lipoprotein cholesterol.[13]

The combination of hypertension, glucose intolerance, and dyslipidemia significantly increases the risk of cardiovascular events such as myocardial infarction, stroke, and heart failure.[14] Patients with primary hypercortisolism are at a higher risk of cardiovascular morbidity and mortality compared to the general population.

Neuropsychiatric Symptoms

Patients with primary hypercortisolism frequently experience mood disorders, including depression, anxiety, irritability, and emotional lability.[15] These mood changes are likely due to cortisol's effects on the central nervous system, particularly the hippocampus and amygdala.

Cognitive deficits, particularly in memory, attention, and executive function, are also common in hypercortisolism. Patients may report difficulties with concentration, decision-making, and recalling information. These cognitive impairments are often reversible with successful treatment of hypercortisolism, though some deficits may persist, especially in long-standing cases.

Sleep disturbances, including insomnia and fragmented sleep, are frequently reported by patients with primary hypercortisolism. These issues may be exacerbated by the mood disorders and cognitive impairments associated with the condition.

Bone and Musculoskeletal Symptoms

Chronic cortisol excess leads to a significant decrease in bone mineral density, resulting in osteoporosis.[16] Patients with primary hypercortisolism are at a high risk for osteoporotic fractures, particularly in the vertebrae, ribs, and hips. The mechanism involves cortisol-induced inhibition of

osteoblast function, increased bone resorption, and decreased calcium absorption.

Aseptic necrosis of the femoral head, also known as avascular necrosis, is a less common but serious complication of hypercortisolism. This condition occurs due to reduced blood flow to the bone, leading to bone death and joint destruction, and may require surgical intervention.

Reproductive and Endocrine Manifestations

Women with primary hypercortisolism often experience menstrual irregularities, including oligomenorrhea (infrequent menstruation), amenorrhea (absence of menstruation), and infertility. These disturbances are primarily due to cortisol's inhibitory effect on the hypothalamic-pituitary-gonadal axis, leading to decreased secretion of gonadotropins and disruption of normal ovarian function. In some women, primary hypercortisolism may lead to hyperandrogenism, manifesting as hirsutism, acne, and, in severe cases, virilization (development of male secondary sexual characteristics). This occurs due to the overproduction of adrenal androgens, which can occur alongside excess cortisol production in adrenal tumors.

In men, hypercortisolism can lead to hypogonadism, characterized by reduced libido, erectile dysfunction, and decreased sperm production. This occurs due to cortisol's suppressive effects on the secretion of luteinizing hormone and follicle-stimulating hormone, as well as direct effects on testicular function.

Immunologic and Hematological Effects

Cortisol has potent immunosuppressive effects, which can lead to an increased susceptibility to infections.[17] Patients with primary hypercortisolism may experience recurrent infections, particularly bacterial and fungal infections, and delayed wound healing.

Hematological abnormalities, such as leukocytosis (elevated white blood cell count) and lymphopenia (reduced lymphocyte count), are common in primary hypercortisolism. These changes reflect cortisol's effects on the redistribution of immune cells and its suppression of lymphocyte production.

Hypercoagulability is a recognized complication of hypercortisolism, leading to an increased risk of venous thromboembolism, including deep vein thrombosis and pulmonary embolism (PE).[18,19] The exact mechanisms are complex but involve increased levels of clotting factors, decreased fibrinolysis, and vascular endothelial dysfunction.

Other Clinical Manifestations

Gastrointestinal symptoms, such as peptic ulcer disease, gastroesophageal reflux disease, and abdominal pain, can occur in primary hypercortisolism. Cortisol stimulates gastric acid secretion and impairs the mucosal barrier, increasing the risk of ulcers and erosions.

Hypercortisolism can increase the risk of kidney stones, particularly calcium oxalate stones, due to hypercalciuria (increased urinary calcium excretion) and hypocitraturia (low urinary citrate levels), both of which are influenced by cortisol levels.

Fatigue is a common, nonspecific symptom in primary hypercortisolism, likely related to a combination of metabolic disturbances, muscle weakness, and neuropsychiatric effects.

In some patients, primary hypercortisolism may present in a subclinical form,[20] where cortisol levels are mildly elevated, but the classical signs and symptoms of Cushing's syndrome are not overtly apparent. This condition is often detected incidentally during evaluation for other conditions, such as hypertension or osteoporosis.

DIAGNOSTIC EVALUATION

The diagnostic evaluation of primary hypercortisolism is a complex process that involves confirming the presence of hypercortisolism, differentiating it from other causes of Cushing's syndrome, and identifying the specific etiology responsible for cortisol overproduction.[21] The diagnosis requires a combination of clinical assessment, biochemical tests, imaging studies, and in some cases, genetic testing.[22]

Clinical Assessment—History and Physical Examination

The diagnostic process begins with a detailed clinical history and physical examination.[23] Patients may present with a variety of symptoms, including weight gain, central obesity, hypertension, muscle weakness, skin changes (such as purple striae), and menstrual irregularities. A thorough history should also explore the duration and progression of symptoms, as well as any use of exogenous glucocorticoids, which could suggest an iatrogenic cause of Cushing's syndrome.

The physical examination should focus on signs suggestive of Cushing's syndrome, such as a *moon face*, *buffalo hump*, thin skin, easy bruising, and proximal muscle weakness. Identifying these features can raise suspicion for hypercortisolism and prompt further investigation.

Biochemical Testing

Biochemical testing is essential to confirm the presence of hypercortisolism and to differentiate between ACTH-dependent and ACTH-independent causes.[24] The following tests are commonly used in the diagnostic evaluation, and are summarized in **Table 1**.

Initial screening tests

The 24-Hour Urinary Free Cortisol (UFC) test measures the amount of cortisol excreted in the urine over 24 hours. This test reflects the total cortisol production and is a reliable indicator of hypercortisolism. Elevated UFC levels above the normal reference range are suggestive of hypercortisolism. However, the test may be less sensitive in mild cases or in patients with renal impairment, which can affect cortisol clearance.

The late-night salivary cortisol (LNSC) test measures cortisol levels in saliva collected late at night, typically around 11:00 PM Cortisol production follows a circadian rhythm, with levels peaking in the morning and reaching a nadir at night.[25] Elevated LNSC levels suggest a loss of the normal diurnal variation in cortisol secretion, which is characteristic of Cushing's syndrome. This test is noninvasive and particularly useful for detecting mild or cyclical forms of hypercortisolism.

The low-dose dexamethasone suppression test (LDDST) involves administering a low dose of dexamethasone (1 mg) at 11:00 PM, followed by measurement of serum cortisol levels at 8:00 AM the next morning. Dexamethasone is a synthetic glucocorticoid that should suppress cortisol production in healthy individuals. Failure to suppress serum cortisol levels (typically defined as >1.8 μg/dL or 50 nmol/L) after dexamethasone administration suggests the presence of Cushing's syndrome. The LDDST is sensitive and widely used in clinical practice.

Confirmatory tests

If initial screening tests indicate hypercortisolism, confirmatory tests are performed to strengthen the diagnosis and help determine the cause.

The high-dose dexamethasone suppression test (HDDST) involves administering a higher dose of dexamethasone (8 mg) and measuring cortisol levels. This test helps differentiate between ACTH-dependent and ACTH-independent causes. In ACTH-independent hypercortisolism, cortisol levels will not be suppressed by high-dose dexamethasone. In contrast, some ACTH-dependent

Table 1
Diagnostic tests for primary hypercortisolism

Initial Screening Tests	How It Is Done	Interpretation
24-h UFC	Amount of cortisol excreted in the urine over 24 h	Elevated UFC levels are suggestive of hypercortisolism
LNSC	Cortisol levels in saliva at night, typically around 11:00 PM	Cortisol production follows a circadian rhythm, with levels peaking in the morning and reaching a nadir at night
LDDST	1 mg of dexamethasone at 11:00 PM, measurement of serum cortisol levels at 8:00 AM the next morning	Failure to suppress serum cortisol levels (typically defined as >1.8 μg/dL or 50 nmol/L) after dexamethasone administration suggests the presence of Cushing's syndrome.
Confirmatory Tests		
HDDST	Like LDDST, with 8 mg of dexamethasone	Differential between ACTH-independent (cortisol not suppressed by high-dose dexamethasone) and ACTH-dependent (cortisol may show partial suppression) causes.
Midnight Serum Cortisol	Cortisol levels in serum. Usually done in hospital setting.	Elevated midnight serum cortisol levels are highly suggestive of Cushing's syndrome.
Plasma ACTH measurement	ACTH levels in plasma	Differential between ACTH-independent (ACTH <5 pg/mL) vs ACTH-dependent (ACTH ≥5 pg/mL) cause.

causes, such as pituitary adenomas, may show partial suppression.

The midnight serum cortisol is measured during the time when cortisol levels should be at their lowest (nadir).[26] This test is usually performed in a hospital setting. Elevated midnight serum cortisol levels are highly suggestive of Cushing's syndrome and reflect the disruption of the normal diurnal rhythm of cortisol secretion.

The plasma ACTH measurement helps determine whether hypercortisolism is ACTH-dependent or ACTH-independent. Low or undetectable ACTH levels (<5 pg/mL) suggest an ACTH-independent cause, such as an adrenal adenoma, carcinoma, or bilateral adrenal hyperplasia. In contrast, elevated or normal ACTH levels indicate an ACTH-dependent cause, necessitating further evaluation.

Imaging Studies

Imaging studies play a critical role in localizing the source of cortisol overproduction once biochemical testing indicates primary hypercortisolism.

Adrenal imaging

Computed tomography (CT) scan of the adrenal glands is the preferred modality for identifying adrenal tumors, such as adenomas or carcinomas, as well as hyperplasia.[27] In primary hypercortisolism, a unilateral adrenal mass suggests an adenoma or carcinoma. Bilateral adrenal masses or nodular hyperplasia are indicative of conditions such as PBMAH or PPNAD. Alternatively, MRI provides high-resolution images of the adrenal glands and may be used as an adjunct to CT, particularly in cases where the nature of the adrenal mass is uncertain. MRI is also useful in differentiating between benign and malignant lesions. Adenomas typically appear as well-defined, homogenous lesions with specific imaging characteristics, while carcinomas may be irregular, with signs of invasion or metastasis.

Additional imaging

Adrenal Venous Sampling is an invasive procedure that involves sampling blood from the adrenal veins to measure cortisol levels. This test is useful in distinguishing between unilateral and bilateral adrenal disease, especially in cases where imaging results are equivocal.[28] A significant gradient in cortisol levels between the 2 adrenal glands suggests a unilateral lesion, such as an adenoma, while similar cortisol levels on both sides suggest bilateral hyperplasia.

Finally, PET scans, often combined with CT (PET-CT), may be used in cases where adrenal carcinoma is suspected, as this modality can detect metabolic activity indicative of malignancy and metastasis.

Differential Diagnosis

Differentiating primary hypercortisolism from other forms of Cushing's syndrome, as well as from conditions that mimic hypercortisolism, is essential.[29] **Table 2** describes the most common characteristics of these conditions.

- ACTH-Dependent Cushing's Syndrome

Table 2
Differentials for primary hypercortisolism

	Laboratory	Imaging
ACTH-independent Cushing's syndrome (Primary hypercortisolism)	High cortisol Low ACTH levels	Adrenal masses or nodular hyperplasia
ACTH-dependent Cushing's syndrome		
• Cushing's disease (Pituitary adenoma)	High cortisol Elevated or normal ACTH levels	Pituitary adenoma
• Ectopic ACTH Syndrome	High cortisol High ACTH levels Lack of suppression on the HDDST.	Nonpituitary tumor
Pseudo-Cushing's states	Similar to primary hypercortisolism but derived from other conditions (eg, obesity, alcoholism, depression, and poorly controlled diabetes)	-
Iatrogenic Cushing's Syndrome (exogenous glucocorticoids)	Similar to primary hypercortisolism	-

- Cushing's disease (Pituitary Adenoma): Distinguished by elevated or normal ACTH levels and pituitary imaging revealing an adenoma.
- Ectopic ACTH syndrome: Characterized by high ACTH levels, often from a nonpituitary tumor, and typically a lack of suppression on the HDDST.

- Pseudo-Cushing's states: Conditions such as obesity, alcoholism, depression, and poorly controlled diabetes can cause biochemical abnormalities similar to those seen in Cushing's syndrome.[30,31] These states usually resolve upon treatment of the underlying condition, and cortisol levels normalize.
- Iatrogenic Cushing's syndrome: Chronic use of exogenous glucocorticoids is the most common cause of iatrogenic Cushing's syndrome. A detailed medication history is essential to identify this condition.

Genetic Testing

Genetic testing is increasingly important in the diagnostic evaluation, particularly in cases of primary hypercortisolism associated with genetic syndromes or familial occurrence.[7]

In suspected cases of PPNAD or Carney complex, genetic testing for PRKAR1A mutations can confirm the diagnosis and guide management. A positive test for PRKAR1A mutations supports the diagnosis of PPNAD or Carney complex, and may prompt screening for other associated tumors and conditions.

In patients with PBMAH, particularly those with a family history of adrenal disorders, genetic testing for armadillo repeat containing 5 (ARMC5) mutations can be informative. Identification of ARMC5 mutations supports the diagnosis of PBMAH and may have implications for family members.

In patients with McCune-Albright syndrome or other syndromes associated with hypercortisolism, testing for GNAS mutations can confirm the diagnosis. A positive GNAS mutation indicates the presence of McCune-Albright syndrome and helps in understanding the broader clinical picture, including other potential endocrine abnormalities.

DISEASE MANAGEMENT

Management primarily aims to normalize cortisol levels and address the underlying cause of excess cortisol production.[22,32]

Surgical Management

Adrenalectomy is the treatment of choice for most cases of primary hypercortisolism, especially if an adrenal adenoma or carcinoma is identified.[32,33] After adrenalectomy, patients often need temporary glucocorticoid replacement therapy because the normal adrenal gland may be suppressed.[32,34]

Pharmacologic Management

Pharmacologic interventions are usually employed when surgery is not feasible (due to contraindications or patient refusal) or as a preoperative or adjunct treatment to control cortisol levels.[35,36] The drugs used aim to inhibit cortisol production, block cortisol action, or modulate the pituitary-adrenal axis.[34,37]

Steroidogenesis inhibitors

These medications reduce cortisol production by inhibiting the enzymes involved in its biosynthesis in the adrenal glands. Ketoconazole (first-line drug) inhibits multiple enzymes in the cortisol synthesis pathway, including 17α-hydroxylase and 11β-hydroxylase. Among side effects, patients may experience hepatotoxicity, gastrointestinal disturbances, gynecomastia (due to its antiandrogenic effects). Metyrapone inhibits 11β-hydroxylase, an enzyme essential for cortisol synthesis. It may cause hirsutism (due to increased androgen precursors), hypertension, and/or electrolyte disturbances. Etomidate is used in critical situations for rapid control of cortisol levels. It inhibits 11β-hydroxylase and is administered intravenously. Typically reserved for acute, severe cases of hypercortisolism (eg, life-threatening situations). Osilodrostat is a newer agent that inhibits 11β-hydroxylase, approved for the treatment of Cushing's syndrome, especially in patients who are not candidates for surgery.

Adrenolytic agents

Mitotane is a cytotoxic drug that inhibits adrenal cortisol synthesis and destroys adrenal tissue. It is primarily used for adrenal carcinomas but can also be used in cases of hypercortisolism. It has a slow onset of action and long-lasting effects but can lead to adrenal insufficiency. Known side effects are nausea, vomiting, diarrhea, and cognitive disturbances.

Glucocorticoid receptor antagonists

Mifepristone (RU-486) is a glucocorticoid receptor antagonist that blocks the action of cortisol at the receptor level, particularly useful in managing the metabolic effects of hypercortisolism, such as hyperglycemia (often in patients with Cushing's syndrome and diabetes). Among possible side effects: fatigue, nausea, hypokalemia, potential for adrenal insufficiency (though cortisol levels remain high).

Adjunctive and Supportive Management and Follow-up

Management of complications

Hypercortisolism often leads to complications such as diabetes, hypertension, osteoporosis, and infections that may require concurrent management.[9,38] For instance, use of antihypertensive agents like angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, or insulin/oral hypoglycemic agents. With regards to osteoporosis, bisphosphonates or other agents like denosumab can be considered to prevent or treat bone loss. Finally, Cushing's syndrome often results in psychiatric symptoms such as depression, anxiety, and cognitive disturbances, requiring psychological support or pharmacotherapy.

Follow-up and monitoring

The management of primary hypercortisolism demands regular monitoring of cortisol levels as it is essential to ensure adequate control of hypercortisolism. ACTH levels monitoring is needed in cases where the pituitary is involved (though this is more relevant to secondary hypercortisolism). Regular imaging studies may be necessary in cases of adrenal carcinoma or nodular hyperplasia to evaluate tumor size and recurrence.

SUMMARY OF TREATMENT APPROACH

1. First-line treatment: Surgery (adrenalectomy).
2. Preoperative or non-surgical candidates
   a. Steroidogenesis inhibitors (ketoconazole, metyrapone, osilodrostat).
   b. Adrenolytic agents (mitotane for adrenal carcinoma).
   c. Glucocorticoid receptor antagonists (mifepristone).
3. Adjunctive treatments: Address metabolic complications (hypertension, hyperglycemia, and osteoporosis).
4. Posttreatment monitoring: Ongoing cortisol and ACTH levels, imaging, and management of side effects and comorbidities.

By individualizing the pharmacologic approach to the patient's needs, the goal is to achieve optimal cortisol control while minimizing side effects.[22]

CLINICS CARE POINTS

- *Early diagnosis is key*: Timely identification of primary hypercortisolism is crucial as prolonged cortisol excess can lead to severe complications like cardiovascular disease, diabetes, and osteoporosis. Regular screening in high-risk populations, such as those with unexplained hypertension or glucose intolerance, can help in early detection and reduce morbidity.
- *Cortisol testing*: A stepwise diagnostic approach is essential. Start with initial cortisol tests like 24-h urinary free cortisol, late-night salivary cortisol, or a low-dose dexamethasone suppression test to establish cortisol excess. Multiple abnormal results strengthen the diagnosis of hypercortisolism before moving forward with imaging to localize the cause.
- *Imaging considerations*: Once biochemical tests confirm cortisol excess, imaging studies like computed tomography or MRI of the adrenal glands should be employed to identify the presence of adrenal tumors or hyperplasia. These imaging modalities are critical for distinguishing between benign and malignant adrenal masses and planning further intervention.
- *Monitor for complications*: Due to the multisystem effects of excess cortisol, patients are at high risk for complications like hypertension, dyslipidemia, hyperglycemia, and bone loss. Ongoing monitoring and management of these conditions, through antihypertensive medications, glucose control, and bone health management, are crucial to reducing long-term adverse outcomes.
- *Postsurgical care*: Following adrenalectomy for tumor removal, there is a risk of adrenal insufficiency since the remaining adrenal gland(s) may not immediately produce sufficient cortisol. Careful postoperative monitoring, with regular cortisol testing and appropriate glucocorticoid replacement therapy, is vital to prevent adrenal crisis and ensure smooth recovery.
- *Differentiation from adrenocorticotropic hormone (ACTH)-dependent causes*: It's critical to rule out ACTH-dependent hypercortisolism (eg, Cushing's disease from a pituitary adenoma) before pursuing adrenal-focused treatments. This differentiation prevents unnecessary adrenal surgeries in cases where the root cause lies in the pituitary or elsewhere, such as ectopic ACTH-producing tumors.

DISCLOSURES

The authors have nothing to disclose.

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