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Review Article

Drug induced iatrogenic Cushing's syndrome

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ABSTRACT

Drug-induced (iatrogenic) Cushing's syndrome results from excessive or prolonged exposure to glucocorticoids, commonly prescribed for autoimmune, inflammatory, and hematological disorders due to their anti-inflammatory, immunosuppressive, and proapoptotic effects. Despite their therapeutic benefits, these medications can lead to a range of multisystemic symptoms mirroring those of endogenous Cushing's syndrome. This review aims to elucidate the causes, clinical presentation, diagnosis, and management of iatrogenic Cushing's syndrome, emphasizing awareness of medications that can trigger its onset. The following review covers cortisol physiology, Cushing's syndrome etiology and subtypes, hypercortisolism complications and prognosis, and strategies for glucocorticoid withdrawal. This article synthesizes key findings and recommendations, highlighting challenges and controversies in the diagnosis and treatment of iatrogenic Cushing's syndrome.

Keywords: Iatrogenic Cushing's syndrome, Glucocorticoids, Hypercortisolism, Endogenous Cushing's syndrome, Glucocorticoid-induced disorders, Glucocorticoid withdrawal

INTRODUCTION

Cushing's syndrome (CS) is an endocrinological disorder characterized by an excess of glucocorticoids, either dependent or independent of adrenocorticotropic hormone (ACTH). Iatrogenic (exogenous) Cushing's syndrome is the most common variant of hypercortisolism encountered in clinical practice by healthcare professionals. In cases of non-ACTH-related chronic hypercortisolism, an inhibition of corticotropin-releasing hormone (CRH) and ACTH secretion is observed due to negative feedback. For this group, it is recommended to consider the possibility of examining the presence of lesions in the adrenal glands, either unilateral (adenoma or carcinoma) or bilateral (macro or micronodular adrenal hyperplasia), especially in children under 5 years old.

It often leads to a severe clinical presentation and may be manifested after the treatment of diseases where the anti-inflammatory, immunosuppressive, and proapoptotic effects of glucocorticoids are overly pronounced. This is evident in autoimmune, hematological, and inflammatory conditions (such as autoimmune diseases, rheumatoid arthritis, inflammatory bowel disease, and inflammatory skin disease). These drugs are available in a wide variety of forms, ranging from tablets to intravenous (IV) administration, joint injections, enemas, skin creams, inhalers, and eye drops.[1]

These drugs are glucocorticoid receptor agonists that activate glucocorticoid receptors in lymphocytes, achieving an anti-inflammatory effect. However, since glucocorticoid receptors are not exclusive to lymphocytes, glucocorticoid treatment will inevitably stimulate

receptors present in various cell types in the body, including the skin, muscles, bones, blood vessels, pituitary gland, and brain cells. This gives rise to what is often known as the "side effects" of glucocorticoids, including weight gain, rounded face, skin fragility with a tendency to bruise, decreased muscle mass, osteoporosis, hypertension, and diabetes. These side effects are identical to the signs produced by overstimulation of the same glucocorticoid receptors due to elevated levels of endogenous cortisol in Cushing's syndrome. Although hypertension is common, hypokalemia is less frequent than in spontaneous cases because synthetic glucocorticoids have a less pronounced mineralocorticoid activity compared to natural cortisol.

Physicians prescribing glucocorticoid treatments must be aware that it can induce a certain degree of Cushing's syndrome, which is often dose-dependent and influenced by the duration and sensitivity of the patient.

The most crucial aspect in the management of iatrogenic Cushing's syndrome is the careful withdrawal of glucocorticoids. Discontinuing a short-term corticosteroid therapy lasting weeks or, at most, a few months, does not generally pose significant issues. However, withdrawing long-term treatment, persisting for several months or even years, presents a challenge for both the patient and the treating physician.[1]

JUSTIFICATION

Given that glucocorticoids are widely utilized medications for treating a variety of diseases, iatrogenic Cushing's syndrome poses a significant public health concern. Investigating this syndrome is essential to comprehend its prevalence and risk factors, potentially leading to improved clinical practices and a reduction in cases.

Iatrogenic Cushing's syndrome can have a substantial impact on the quality of life for patients, as it is associated with a variety of adverse effects. Research can contribute to increased awareness and education, both among healthcare professionals and patients, regarding the safe use of glucocorticoids in clinical practice, associated risks, symptoms, and the treatment of iatrogenic Cushing's syndrome. This, in turn, can lead to earlier detection and more appropriate care.

Objective

Provide information on the causes of iatrogenic Cushing's syndrome and the importance of being aware of the medications that can cause it.

THEORETICAL FRAMEWORK

Understanding the physiology of cortisol is pivotal in grasping its role within our physiological milieu and comprehending how its dysregulation can contribute to the pathogenesis of disorders, notably Cushing's syndrome.

The adrenal glands are responsible for secreting cortisol in the human body. This hormone is released in response to stress; the hypothalamus releases CRH, which stimulates the pituitary gland to release ACTH.[2]

Cortisol serves several crucial functions in our body, including the regulation of carbohydrate and protein metabolism. It participates in increasing the release of glucose into the bloodstream, a process known as gluconeogenesis. It suppresses the body's immune response, thereby reducing inflammation. Cortisol follows a circadian rhythm, with higher levels in the morning and lower levels at night, aiding in maintaining wakefulness during the day, facilitating daily activities, and promoting sleep at night.[2]

The oversecretion of cortisol by the adrenal glands sets off a cascade of hormonal effects, resulting in Cushing's syndrome. Hypercortisolism can arise from various etiologies, such as: pituitary adenomas secreting large amounts of ACTH, causing adrenal hyperplasia, abnormal hypothalamic function causing high levels of corticotropin-releasing hormone, ectopic secretion of ACTH by a tumor elsewhere in the body, adrenal cortex adenomas, and prolonged administration of corticosteroids.[2]

Primary overproduction of cortisol by the adrenal glands accounts for approximately 20 to 25% of Cushing's syndrome cases.[3]

This syndrome can be classified as either ACTH-dependent or ACTH-independent. ACTH-dependent Cushing's syndrome is characterized by chronic hypersecretion of ACTH, leading to hyperplasia of the fasciculate and reticular zones of the adrenal glands. This, in turn, results in an increased secretion of cortisol and androgens. On the other hand, ACTH-independent Cushing's syndrome can be caused by the presence of a primary adrenal neoplasm (either an adenoma or a carcinoma) or bilateral nodular adrenal hyperplasia. In this case, excess cortisol suppresses the secretion of ACTH in the pituitary.[4]

Incidence and subtypes

Cushing's disease has been the most frequent, accounting for 80% of cases. There is a significantly higher incidence in women than in men, approximately 5 to 1. It is typically diagnosed between the ages of 20 and 40.[4]

Ectopic ACTH hypersecretion accounts for 10% of the patients with ACTH-dependent Cushing's syndrome. When ACTH is produced due to a non-pituitary tumor, it can cause severe hypercortisolism. Interestingly, many of these patients do not exhibit classic glucocorticoid excess characteristics, likely due to the acute clinical course of this syndrome with ectopic hormone secretion. Tumors in these cases are often of thoracic origin, with bronchial and pulmonary carcinoma accounting for over 50% of cases.

Prognosis for these patients is often unfavorable, largely attributed to the primary tumor. This type of syndrome may resemble classic Cushing's disease, posing diagnostic challenges. It is more common in men, with a higher incidence between 40 and 60 years of age.[4,5]

Primary adrenal tumors, typically benign adrenocortical adenomas, are also relevant causes of Cushing's syndrome. Adrenocortical carcinoma is less common, with a higher occurrence in females. Autonomous cortisol secretion without classic Cushing's features can be observed in 20 to 25% of patients with adrenal incidentalomas.[4]

A rare subtype of Cushing's syndrome occurs in children, more commonly in adolescents or children older than 10, affecting both genders equally. A key feature of this pediatric Cushing's syndrome is significant weight gain without proportional linear growth.[4]

Clinical presentation and diagnosis

The suspicion of Cushing's syndrome in patients arises in the presence of central obesity with accumulation of supraclavicular fat, a cervical fat pad, thinning of the skin, violaceous striae, proximal muscle weakness, fatigue, arterial hypertension, glucose intolerance, acne, hirsutism, and menstrual irregularities. Neuropsychological disturbances are also frequently observed, including depression, emotional irritability, sleep disturbances, and cognitive deficits.[3]

The diagnosis of Cushing's syndrome involves a two-step process: endogenous hypercortisolism must first be confirmed and then its cause should be determined. Currently, there are no clinical tools for accurately measuring the severity of the disease. Although correlations with urinary cortisol levels and two globally recognized severity scales exist, these have proven more useful for endogenous Cushing's syndrome and less so for iatrogenic Cushing's cases.[6]

The evaluation of the pituitary-adrenal axis has been extensively used to confirm Cushing's syndrome diagnoses. However, however it has not demonstrated complete capability in distinguishing all cases of Cushing's syndrome from normal individuals.[3]

Table 1: Differential diagnosis of Cushing syndrome.

Differential diagnosis of Cushing syndrome	Normal	Primary hypercortisolism	Ectopic ACTH secretion	Cushing disease
ACTH levels	↔	↓	↑	↑
Low-dose dexamethasone suppression test	Cortisol ↓	Cortisol↔	Cortisol↔	Cortisol↔
High-dose dexamethasone suppression test	Cortisol ↓	Cortisol↔	Cortisol↔	Cortisol ↓
CRH and desmopressin stimulation tests	ACTH↑ Cortisol↑	Cortisol↔ ACTH↔	Cortisol↔ ACTH↔	ACTH↑ Cortisol↑

Chronic corticosteroid exposure and Cushing's syndrome

Chronic exposure to corticosteroids can lead to Cushing's syndrome. These medications, commonly prescribed today, are given to approximately 3% of patients with various diseases due to their potent immunosuppressive and anti-inflammatory properties. They are also utilized as replacement therapy in patients with adrenal insufficiency.[7]

Glucocorticoids are considered lipophilic substances that bind to receptors in the cell cytoplasm, influencing glucose production and utilization. For example, they increase gluconeogenesis in the liver, potentially causing side effects such as hyperglycemia, prediabetes, and worsening conditions in patients with diabetes mellitus. These effects can contribute to a higher susceptibility to infections, leading to a deterioration of the underlying disease.[7]

Furthermore, these drugs have both lipolytic and lipogenic effects, resulting in increased visceral adipose tissue and decreased subcutaneous adipose tissue. This promotes insulin resistance, sharing characteristics with Cushing's syndrome.[7]

Corticosteroids also induce the loss of muscle mass by reducing protein synthesis, impacting the function of pancreatic beta cells, and contributing to beta cell apoptosis, leading to decreased insulin production and increased glucagon secretion.[7]

Corticosteroids act by inhibiting the function of the hypothalamic-pituitary-adrenal axis (HPA), leading to a spectrum of multisystemic symptoms that develop gradually, depending on the duration and dosage of patient use. Common manifestations of this disease include centralized obesity, "moon facies", "buffalo hump", hirsutism, bruising, striae, and acne. Patients may also develop arterial hypertension, insulin resistance, and diabetes mellitus. Additionally, corticosteroids significantly influence bone metabolism, hindering absorption and increasing renal excretion of calcium, thereby affecting other the skeletal system, it can also alter mood, immune response, and the metabolism of carbohydrates, lipids, and proteins.[8]

The use of these medications can induce genetic changes affecting the immune response, hindering the function of innate/humoral immunity during or after usage. Various analyses demonstrate decreased thymic activity, reduced

lymphocytic proliferation, and increased apoptosis of critical regulators induced by glucocorticoids in pediatric patients. Glucocorticoids negatively regulate the transcriptional regulation controlled by NF-kB. The primary cytokine affected by these medications is IL-2, crucial for the humoral response of T lymphocytes, leading to a decrease in their blood levels.[9]

Complications of Cushing's syndrome can affect various organ systems, including persistent moderate arterial hypertension, which may have a multifactorial pathogenesis involving the inhibition or alteration of the vasodilator system and activation of the renin-angiotensin-aldosterone system. Excessive cortisol levels can surpass the capacity of the enzyme 11ß-HSD2, responsible for cortisol inactivation, leading to increased cortisol binding to mineralocorticoid receptors. This results in heightened aldosterone effects and myocardial fibrosis.[10]

Hypercortisolism poses a cardiovascular risk factor, contributing to central obesity, glucose intolerance, hypercoagulability, dyslipidemia, and an increased incidence of atherosclerosis. These factors significantly impact morbidity and mortality, making cardiovascular diseases the leading cause of death in Cushing's syndrome. The cardiovascular risk may persist up to 5 years after hypercortisolism.[10]

Management

When treating iatrogenic Cushing's syndrome, the most crucial aspect is the withdrawal of glucocorticoids. Discontinuing short-term glucocorticoid therapy lasting weeks or even a few months generally does not pose significant problems. However, withdrawing long-term treatment persisting for several months or years presents a challenge for both the patient and the treating physician. The longer the steroid treatment and the higher the dose applied; the more time is needed for withdrawal.[1]

Recovery of the normal functioning of the HPA axis takes over a year. However, maintaining the HPA axis responsiveness is possible by administering a reduced amount of steroids in the morning, as morning ACTH secretion suppression occurs less frequently with this protocol.[1]

The discontinuation of glucocorticoids is only appropriate when the underlying disease is in a long-term inactive phase with a steroid dose corresponding to the daily replacement dose or only slightly exceeding it. In the case of an active disease, alternative effective treatment approaches to control the underlying pathology should be considered instead of glucocorticoids, such as other forms of immunosuppression.[1]

Regarding the type of glucocorticoid used, two main approaches are proposed in this research. One suggests changing the steroid administration to alternate days without modifying the previously prescribed glucocorticoid. It is essential to note that this change in medication intake should not be abrupt, as it could trigger symptoms of adrenal insufficiency on days without the steroid.

On the other hand, another approach suggests using hydrocortisone instead of the previously used synthetic glucocorticoids. Hydrocortisone, sharing a chemical structure similar to the body's natural cortisol, suppresses the HPA axis to a lesser extent compared to other synthetic glucocorticoids. However, due to its shorter biological half-life, hydrocortisone alleviates Cushing's syndrome symptoms. It is important to note that this type of glucocorticoid should be administered at least twice daily.[1]

DISCUSSION

Cushing's syndrome results from an overproduction of cortisol and can occur for various reasons, such as pituitary adenomas secreting excessive amounts of ACTH, abnormal functions in the hypothalamus, adrenal gland adenomas, or prolonged use of corticosteroids.[2]

Approximately 20 to 25% of Cushing's syndrome cases are related to the primary overproduction of cortisol by the adrenal glands. Cushing's disease accounts for about 80% of cases, with a higher prevalence in women than in men, in a ratio of 5:1. Diagnoses are typically made between the ages of 20 and 40.[4]

In 10% of patients with ACTH-dependent Cushing's syndrome, there is ectopic overproduction of ACTH. This can cause severe hypercortisolism, as these patients do not exhibit the classic characteristics of glucocorticoid excess.[4,5]

Misuse of glucocorticoids can lead to this syndrome, potentially impacting the immune system by triggering genetic changes. There may be a diminished response of the innate or humoral immune response. A decrease in T-cell activity, lymphocyte proliferation, and an increase in apoptosis of critical regulators in response to glucocorticoids have been observed.[9]

The use of these medications can lead to genetic changes that affect the immune response, causing a decrease in the expression of innate or humoral immunity during their use. In pediatric patients, a reduction in thymic activity, lymphocyte proliferation, and an increase in apoptosis of critical regulators induced by glucocorticoids have been observed. These medications negatively regulate the transcriptional regulation governed by NF-kB.[9]

The symptoms and signs of this syndrome include central obesity, supraclavicular fat accumulation, thinning skin, purple striae, muscle weakness, fatigue, hypertension, lactose intolerance, acne, hirsutism, menstrual irregularities, "moon facies", and "buffalo hump". Neuropsychological alterations such as depression, emotional irritability, sleep disturbances, and cognitive

deficits may also be present, along with increased renal calcium excretion.[8]

Diagnosing Cushing's syndrome involves a process where the first step is confirming endogenous hypercortisolism and then determining its cause. Despite worldwide scales correlating cortisol levels in urine with treatment and severity, these techniques have not proven effective in patients with iatrogenic Cushing's syndrome. The pituitary-adrenal axis has traditionally been a more reliable method for confirming the diagnosis.[3]

We analyzed articles discussing iatrogenic Cushing's syndrome. The first article focuses on the severity of endogenous Cushing's syndrome in rheumatological patients using continuous glucocorticoids.[7] On the other hand, the second article presents a case of an 11-year-old girl with psoriasis who developed Cushing's syndrome due to the topical use of corticosteroids for 2 years. A notable similarity is that the use of these medications, regardless of the underlying disease, can lead to adverse effects such as Cushing's syndrome.[6]

Both articles include patients with a history of systemic glucocorticoid use. In the first article, a questionnaire was administered, and consistency, agreement, and principal component analysis were conducted to assess the severity of Cushing's syndrome.

In conclusion, the first article discusses the severity of Cushing's syndrome in patients with rheumatological diseases using glucocorticoids continuously. Meanwhile, the second article presents a case of a girl who developed Cushing's syndrome due to the same cause

CONCLUSION

In conclusion, this research highlights that Cushing's syndrome is characterized by an excess of glucocorticoids, whether related to adrenocorticotropic hormone (ACTH) or not. Iatrogenic Cushing's syndrome, induced by external administration of glucocorticoids, is the most common variant encountered in clinical practice.

Corticosteroids impact the immune system, diminishing the expression of both innate and humoral immunity, leading to a reduction in lymphocytic proliferation. Excessive cortisol levels may surpass the function of the enzyme 11ß-HSD2, responsible for its deactivation. This facilitates cortisol binding to mineralocorticoid receptors, resulting in an increased action of aldosterone and myocardial fibrosis.

Hypercortisolism can also lead to significant complications such as persistent hypertension and an elevated risk of atherosclerosis. This, in turn, contributes to cardiovascular problems, ultimately emerging as the primary cause of death in Cushing's syndrome.

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