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Role of genetic in stimulating Cushing's syndrome in women and children

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Abstract

Pituitary adenomas that secrete corticotropin and form from monoclonal expansion of cortical cells in the anterior pituitary gland are the source of Cushing's disease. These tumors are typically benign. An adrenal tumor, whether benign or malignant, secretes cortisol due to increased endogenous cortisol synthesis, which also results in Cushing's syndrome. Many problems, such as hyperglycemia, aberrant protein catabolism, immunosuppression, anomalies in neurocognition, bone diseases like osteoporosis, and mood disorders like depression, can be brought on by elevated cortisol levels. Therefore, the adrenocorticotropic hormone (ACTH) and genetic molecular pathways causing primary adrenal lesions to secrete excessive amounts of cortisol. Protease 8 (USP8) and USP48 somatic activating genetic variants have been found in roughly 21% to 60% of adenocarcinomas, and 6% to 12% of them, respectively. As a result, the most common Cushing's syndrome can be diagnosed at any age between 5 and 75, although the average diagnosis age is between 30 and 49.

Keyword: Cushing's syndrome; Exogenous CS; Adrenocorticotropic hormone; Steroid hormone; Corticotropin dependent

1. Introduction

Cushing's syndrome defined as excessive cortisol production caused by excess adrenocorticotropic hormone (ACTH) secreted by a cortical adenoma of the pituitary gland (1). As a result of increased endogenous cortisol production, an adrenal tumor, whether benign or malignant, secretes cortisol, which also causes Cushing's syndrome. Ectopic Cushing's syndrome is also caused by a tumor that secretes corticotropin other than the pituitary gland, as less than 1% of patients with Cushing's syndrome suffer from a tumor that secretes corticotrophins-releasing hormone (CRH) (2). As a result, the disease increases the risk of infections, respiratory disorders, psychological concerns, osteoporosis, and symptoms related to the metabolism and cardiovascular system, leading to increased rates of morbidity and death (3).Elevated cortisol can lead to a number of conditions, including hyperglycemia, aberrant protein catabolism, immunosuppression, abnormalities in neurocognition, bone diseases including osteoporosis, and mood disorders like depression. (4) Cushing syndrome typically manifests as weight gain, hypokalemia, and hypertension. More precisely, purple striae, easy bruising, and facial plethora are common symptoms of Cushing syndrome. (5). On the average, there are 0.7–2.4 new instances of Cushing's disease (CD) per million individuals year. while 10% from causes fall into the pediatric age group (1). It rarely occurs in children. Because of their chronic hypercortisolism, which requires early detection and specialized treatment of this serious disease(2).

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2. The epidemiology of Cushing Syndrome

The actual incidence and prevalence of Cushing syndrome are not known. The prevalence of the disease is highly variable across different ethnic and cultural groups depending upon the frequency and spectrum of the medical conditions requiring steroid-based therapy.so the endogenous or external factors can produce childhood and teenage CS. Exogenous CS typically affects kids who need to take Steroid medication; it is likely underdiagnosed, While parenteral or oral glucocorticoid therapy accounts for the majority of cases, administered topically and breathed in children needs special consideration. However the Children are more susceptible to the systemic effects of topically applied glucocorticoids due to their thinner dermis layer of epidermis than adults (6,7), According to multiple studies conducted in Sweden, Denmark, and Korea, there are two to three cases of endogenous Cushing syndrome per million individuals per year(8,9)The It's possible that the US has a higher incidence of Cushing syndrome than other nations. For instance, a research conducted in the US using a health claims database on individuals under 65 years old found that the yearly incidence of Cushing illness was almost 8 per million persons. It is unknown how many people have endogenous Cushing syndrome at this time. Cushing syndrome is thought to be underdiagnosed, nevertheless.(10, 11) The most typical Cushing's syndrome can be diagnosed at any age between 5 and 75 years old, however the average age at diagnosis is between 30 and 49 years old. It is typical for patients to report symptoms for up to three years before Cushing syndrome is diagnosed because many of the symptoms are ambiguous(12). The interval between Cushing's illness may have an even longer time between symptom development and diagnosis(13). While ectopic Cushing syndrome affects both men and women equally, endogenous Cushing syndrome, which is caused by pituitary and adrenal adenomas, affects women roughly three to four times more frequently than males(13,1)

3. Cushing Disease

Cushing's disease is caused by corticotropin-secreting pituitary adenomas that are usually benign and arise from monoclonal expansion of cortical cells in the anterior pituitary gland (14). Nearly 90% of these are microadenomas, defined as less than 10 mm in diameter, most of which are less than 6 mm. millimeter. (15) Large tumors with a diameter of 10 mm or more account for 10% of cortical adenomas. (16,17) Therefore, the genetic and molecular mechanisms responsible for excess cortisol secretion by primary adrenal lesions and adrenocorticotropic hormone (ACTH) secretors or ectopic tumors have been identified. Somatic activating genetic variants of the protease 8 (USP8) gene have been identified in approximately 21% to 60% of adenocarcinomas 21 and the USP48 gene has been identified in approximately 6% to 12%, (18). The Ectopic corticotropin production can be derived from Several types of tumors (7,8). Most patients suffer from ectopy Corticotropin syndrome causes malignant tumors By small cell lung cancer (overt ectopic corticotropin Syndrome). Which leads to hyperpigmentation. Hypertension, Edema, hypokalemia, weakness, glucose, pancreas, lungs, and stomach, medullary thyroid neuroendocrine disorders, corticotropin-secreting malignancies Cushing's fungus is not present in many cases, while anorexia, weight loss, are common signs of Malignant disease , but the source of the neuroendocrine tumor in 8% to 19% of patients has not been identified and may remain unidentified for years. While about 40% of patients suffer from the disease.(19) Adrenal sources of Cushing's syndrome include cortisol-producing adenomas, which are defined as benign adenomas that arise in the fasciculus region of the adrenal cortex. Approximately 28% to 50% are associated with somatic gene variants in the catalytic subunit of protein kinase A (23,20) , They are most prevalent in adults aged 40 to 60 years and children younger than 5 years; In females, it occurs at a rate of 55% to 60%.(21), New biochemical and imaging diagnostic approaches and progress in surgical and radiotherapy techniques have improved the management of patients. The therapeutic goal is to normalise tissue exposure to cortisol to reverse increased morbidity and mortality, Optimum treatment consisting of selective and complete resection of the causative tumor maintenance of pituitary function, and avoidance of tumor recurrence.(22)

4. Pathophysiology

Cortisol is a steroid hormone produced by the zona fasciculate of the adrenal cortex. Which consider is the most potent regulator of corticotropin secretion. Corticotropin derives from a larger precursor pro-opiomelanocortin. Proteolysis occurs at pairs of basic amino acids, generating several peptides, including -lipoprotein and -endorphin (the physiological roles of which are unclear) and corticotropin, which specifically stimulates the adrenalcortex.1Cortisol, (19) that synthesized and secreted by the adrenal cortex, is carried to different parts of the body by cortisol binding protein, almost 90% of cortisol binds to this (CBG) protein and has a bioavailability of 60% to 100%. The mechanisms of Cushing’s syndrome can be divided into those dependent and not dependent on corticotropin (Table 1).(2)

Table 1 Causes of hypercortisolism

Corticotropin dependent	Corticotropin independent
Pituitary-dependent Cushing's syndrome (Cushing's disease)	Adrenal adenoma
Ectopic corticotropin syndrome (bronchial, thymic, pancreatic	Adrenal carcinoma
Ectopic CRH syndrome	Macronodular adrenal hyperplasia
Macronodular adrenal hyperplasia (autonomous)	Micronodular adrenal hyperplasia (including the Carney complex)
Iatrogenic: treatment with corticotropin or its analogues	Adrenal hyperplasia caused by abnormal adrenal expression and function of receptors for various hormones (gastric inhibitory polypeptide, vasopressin, adrenergic agonists, interleukin 1)

While the Synthetic corticosteroids have varying bioavailability and potency, but all affect similar pathways. It is a catabolic hormone that is released under stressful conditions. The excess of cortisol results in an increased rate of gluconeogenesis, glycogenolysis and increases insulin resistance (24) . Cortisol is a steroid hormone, and it directly affects the transcription and translation of enzyme proteins involved in the metabolism of fats, glycogen, proteins synthesis, and Krebs's cycle.(It promotes the production of free glucose in the body, elevating glucose levels, while simultaneously increasing insulin resistance. (25) The destruction of protein yields amino acids which are used in gluconeogenesis. The prolonged catabolism of proteins causes purplish striae of the torso, osteoporosis, and poor wound healing. All these processes involve collagen which is a three amino-based protein. High cortisol levels also cause immune disruptions; this hormone leads to a decrease in lymphocyte levels and increases the neutrophils (26). It causes detachment of marinating pool of neutrophils in the bloodstream and increases the circulating neutrophil levels although there is no increased production of the neutrophils. This mechanism explains the typical picture of raised TLC where there is decreased lymphocyte number and increased neutrophils. The corticosteroids mediate the down regulation of NF-kappa B, regulation of AMP kinase, glycogen phosphorylate, superoxide dismutase, and many other enzymes. Cortisol inhibits the production of IL-2, TNF alpha, IFN alpha, and gamma. Decreased IL-2 levels prevent the proliferation of T-lymphocytes.[9]

5. Conclusion

In Cushing's syndrome, a pituitary corticotroph adenoma—a benign tumor that develops from the monoclonal proliferation of cortical cells in the anterior pituitary gland—secretes excess adrenocorticotropic hormone (ACTH), which causes an excess of cortisol to be produced. The ideal course of treatment includes avoiding tumor recurrence, maintaining pituitary function, and removing the causing tumor completely and selectively.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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