EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 10
154-160
Year: 2021

A BRIEF REVIEW ON CUSHING'S SYNDROME

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Article Received on 02/08/2021 **Article Revised on 23/08/2021** **Article Accepted on 12/09/2021**

ABSTRACT
Cushing's disease is the result of excess secretion of adrenocorticotropic hormone (ACTH) by a benign monoclonal pituitary adenoma. The excessive secretion of ACTH stimulates secretion of cortisol by the adrenal glands, resulting in supraphysiological levels of circulating cortisol. The pathophysiological levels of cortisol are associated with hypertension, diabetes, obesity, and early death. Successful resection of the Cushing's Disease-associated ACTH-secreting pituitary adenoma is the treatment of choice and results in immediate biochemical remission with preservation of pituitary function. Accurate and early identification of Cushing's Disease is critical for effective surgical management and optimal prognosis. The authors review the current pathophysiological principles, diagnostic methods, and management of Cushing's syndrome.

KEYWORDS: Cushing's syndrome, Treatment, Diagnosis.

1. INTRODUCTION

Cushing's syndrome is a disorder of adrenocortical hyperfunction in which the level of cortisol hormone is too much over a long period of time. Hyperfunction characterizes a fatty hump between shoulder, a rounded face and pink or purple stretchmark on skin. In other words fat get deposited at face, neck and back. It is also known as 'moon face'.[1][2]

Cushing's syndrome usually affects adults, age grouped 30 to 5-, and also sometimes is seen in children.[3] It affects about three times as many women as men. People who take medicines called glucocorticoids can develop Cushing's syndrome.[4] More than 10 million American take glucocorticoids each year but it's not known how many of them develop Cushing's syndrome.[5]

Cushing's syndrome can be treated by maintaining the level of cortisol to normal.[6] The earlier the treatment, the better the chances for recovery.[7]

1.1 Adrenal Gland

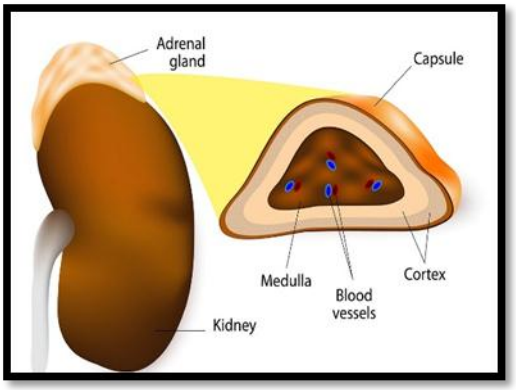


Fig 1: Structure of Adrenal Gland.

Adrenal gland is a small triangular shaped gland, located one on top of each kidneys. It is also known as suprarenal gland. Anatomically adrenal gland gave two parts- *adrenal cortex* and *adrenal medulla.*[8]

Adrenal cortex is the outer region and the largest part of adrenal gland, consist of three layers- *Zonaglomerulosa*, *Zonafasciculata*, *Zonareticularis.* It is responsible for the release of cortisol.[9]

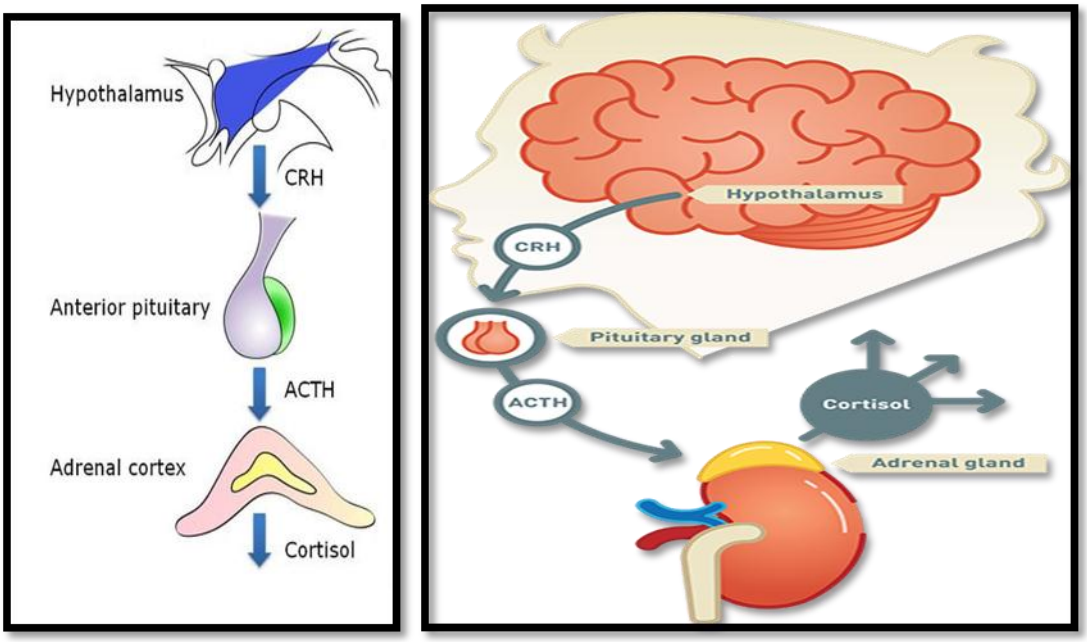
Adrenal medulla is the inner part of the adrenal gland.

1.2Cortisol

Cortisol is a steroid hormone, also known as stress hormone. It is main glucocorticoid released from the zonafasciculata layer of the adrenal cortex.[10] It is synthesized from cholesterol.[11] Cortisol has various function in human body such as.

- Cortisol induces apoptosis of proinflammatory T cells, suppress B cells antibody production and reduce neutrophil migration during inflammation.[12][13]
- It helps in mediating the stress response. Allows the body to continue to stay on high alert. Acutely, cortisol's metabolic mechanism provide energy to body.[14]
- Cortisol monitors the body to maintain homeostasis. It also maintains body fat, protein, carbohydrate. Cortisol control wake/sleep cycle.[15]

1.3 Release of Cortisol



(a) **(b)**

Fig 2 (a) and (b): Adrenal glands produce hormones in response to signals from the pituitary gland in the brain, which reacts to signalling from the hypothalamus, also located in the brain. This is referred to as the hypothalamic pituitary adrenal axis.[16][17]

As an example, for the adrenal gland to produce cortisol, the following occurs:

- The hypothalamus produces corticotropin-releasing hormone (CRH) that stimulates the pituitary gland to secrete adrenocorticotropin hormone (ACTH).[18]
- ACTH then stimulates the adrenal glands to make and release cortisol hormones into the blood.[19]
- Normally, both the hypothalamus and the pituitary gland can sense whether the blood has the appropriate amount of cortisol circulating. If there is too much or too little cortisol, these glands respectively change the amount of CRH and ACTH that gets released. This is referred to as a negative feedback loop.[20]
- Excess cortisol production can occur from nodules in the adrenal gland or excess production of ACTH from a tumor in the pituitary gland or other source.[21]

1.4 Types of Cushing's Syndrome

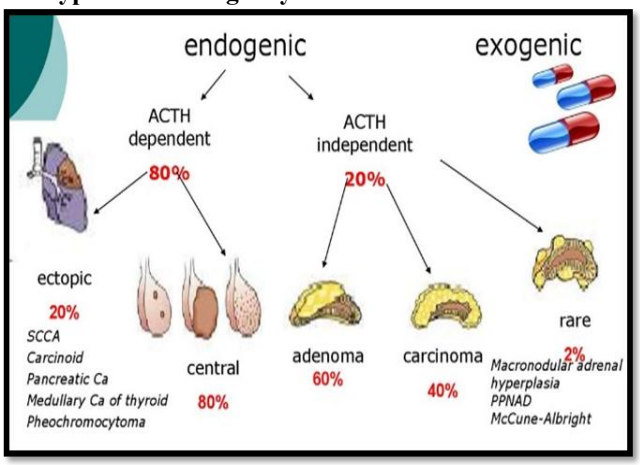


Fig 3: Types of Cushing syndrome.

There are two types of Cushing syndrome: *-exogenous* (caused by factors outside the body) and *endogenous* (caused by factors within the body). The symptoms for both are the same. The only difference is how they are caused.[22]

1.4.1. Exogenous Cushing's Syndrome

Exogenous Cushing's syndrome is a type of Cushing's syndrome which is caused by something outside the body. For example, people consuming glucocorticoid (also known as corticoids or steroid) hormone to treat a disease.[23]

1.4.1.1.Causes of Exogenous Cushion's Syndrome:

Consumption of corticosteroid, such as prednisone in higher dose over time, leads to high production of cortisol hormone in body and develop Exogenous Cushing's syndrome.[24]

Corticosteroids are consumed to cure various diseases such as.

- Oral corticosteroids are used to treat inflammatory diseases like rheumatoid arthritis and lump. Thy may also be used to prevent your body from rejecting a transplanted organ.[25]
- Repeated injecting of corticosteroid to treat joint pain bursitis and back pain.
- Inhaled steroid medicines for asthma and steroid skin cream for skin disorder such as eczema.[26]

1.4.2. Endogenous Cushing's Syndrome

When body produce either too much cortisol or too much adrenocorticotropic hormone (ACTH) which regulates cortisol production. It usually comes on slowly and can be difficult to diagnose.[27]

Endogenous Cushing's syndrome can further be classified into two types.

i. ACTH DEPENDENT DISEASE- In this the level of ACTH is produced in higher amount which stimulated adrenal gland to secret more cortisol.[28]

ACTH dependent disease can be of two types

- Pituitary adenoma- In this a small tumor in pituitary causes increased ACTH production.

It is most common cause of Cushing's syndrome and makes up about 70-80% of cases.[29]

- Ectopic ACTH-producing tumor-bit is a rare form in which the tumor is outside the pituitary makes more ACTH than normal.

This tumor are found in lungs, thyroid, ovary, adrenal gland, liver, thymus gland.[30]

ii. ACTH INDEPENDENT DISEASE- In ACTH independent disease, either both adrenal glands are hyperactive or there is an adrenal tumor that make too much of cortisol.

It causes about 20-30% of Cushing's syndrome cases.[31]

1.4.2.1. Causes of Endogenous Cushing's Syndrome

Endogenous Cushing's syndrome is often caused by hormone-secreting tumors of the adrenal gland or the pituitary, a gland present at the base of brain.[32]

Endogenous Cushing's syndrome may be related to the following causes.

- A Pituitary gland tumor- It is also known as *pituitary adenoma.* It is a non-cancerous (benign) tumor of pituitary gland. It produces excess of ACTH which stimulates over secretion of cortisol. This form of syndrome is called as *Cushing's disease.* It is more commonly found in women.[33]
- An ACTH secreting hormone- This type of tumor can be non-cancerous (benign) or cancerous (malignant). This rarely occurs in an organ which doesn't produce ACTH. Usually found is lungs, pancreas, thyroid or thymus gland.[34]
- A primary adrenal gland disease- In this adrenal cortex produce excess of cortisol which is commonly non-cancerous, called as *adrenal adenoma.*
- Malignant tumor of cortex are rare, but may lead to Cushing's syndrome as well.[35]
- Familial Cushing's syndrome- It is one of rare form where people inherit a tendency to develop a tumor on one or more endocrine glands, affecting cortisol level and causing Cushing's syndrome.[36]

1.5. Epidemiology

Cushing's syndrome is a rare disorder with an annual incidence of 2–3/million of which benign adrenal adenomas account for 0.6/million.[37]

The female:male ratio is 3:1.

More specifically-

- Cushing's syndrome occurs 1.5/million annually.[38]
- Adrenal adenoma occurs 0.6/million annually and is seen more in women as compared to men.
- Adrenal carcinoma has found about 0.2/million annually and 50% Cushing's syndrome in children.[39]
- Ectopic Cushing's syndrome occurs about 1% SSCA, found more in men as compared to women after the age of 50.

Preliminary data indicate a high proportion of subclinical Cushing's syndrome in certain risk populations such as patients with type 2 diabetes or osteoporosis. The clinical implications of these observations are presently unclear.

Surgery remains first line treatment for overt disease and initial cure or remission is obtained in 65–85% of patients with Cushing's disease.[40]

Late recurrences, however, occur in up to 20% and the risk does not seem to plateau even after 20 years of follow-up.

A 2- to 3-fold increase in mortality is observed in most studies, and this excess mortality seems confined to patients in whom initial cure was not obtained.

Cushing's syndrome continues to pose diagnostic and therapeutic challenges and life-long follow-up is mandatory.[41]

1.6. Signs and Symptoms

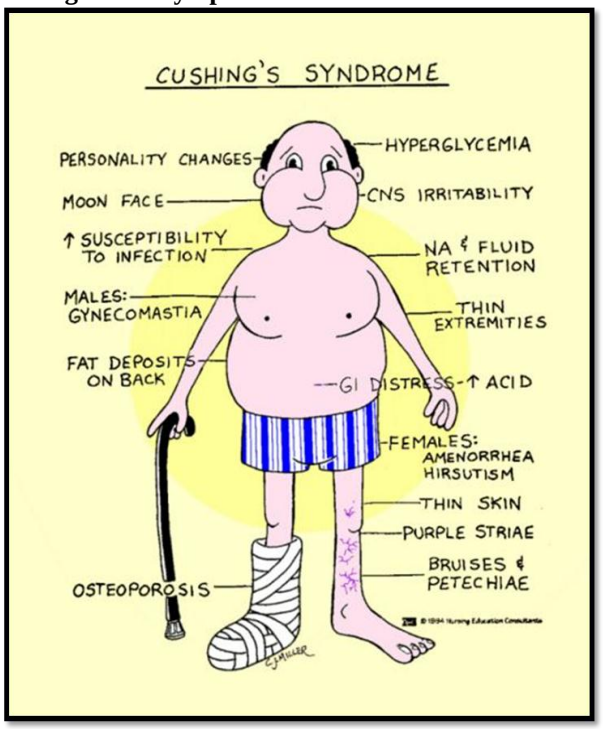


Fig 4: Symptoms of Cushing Syndrome.

The signs and symptoms of Cushing's syndrome depends on various factors such as level of excess cortisol, sex, age etc.

Most common symptoms are[42]

- A round, humpy, red face (moon face)
- Slow growth rate in children
- Central obesity

Skin related symptoms[43]

- Frequent infections
- Pink or purple stretch marks called as striae.
- Thinning of skin

Muscle and bone changes include

- Backache, bone pain and tenderness
- Accumulation of fat between shoulders and neck
- Fractures, week muscles

Systemic problems include

- Type 2 diabetes
- High blood pressure
- High cholesterol and triglycerides

Based on sex

- Irregular or stop of menstruation in women
- Low libido and irrection problem in men

Other symptoms may include

- Mental changes(depression and anxiety)
- Fatigue
- Headache
- Increased thirst and urination.

1.7. Complications

If a person with Cushing's syndrome is not treated, it leads to various complications such as[44]

- Osteoporosis
- Hypertension
- Loss of muscle mass and strength
- Frequent and unusual infection
- Type 2 diabetes.

1.8. Diagnosis

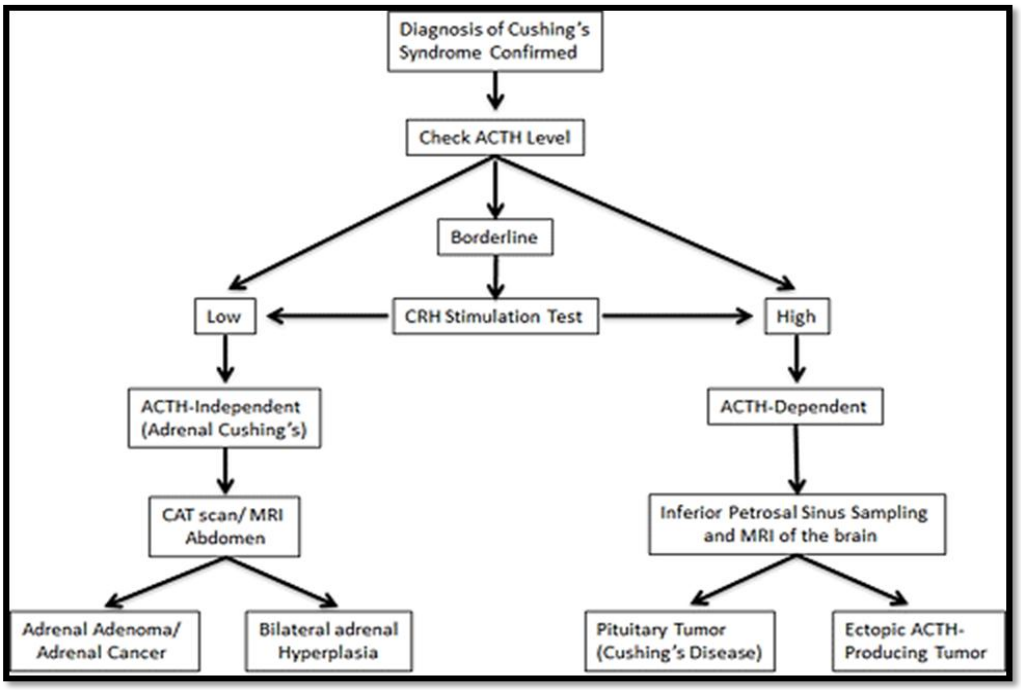


Fig 5: Diagnosis of Cushing Syndrome.

The Cushing's syndrome can be diagnosed by below mentioned test/exams.

24-hour urinary free cortisol test- In this test, the urine for 24 hours is collected and amount of cortisol in it is measured.

Dexamethasone suppression test- The patient is given a low dose steroid pill at 11:00 p.m. and the blood test is done in the morning to know that level of cortisol synthesized by the body in that duration.

Late night salivary cortisol test- This test is performed to measure cortisol in saliva and this test is usually performed at night.

If Cushing's syndrome is diagnosed, further more test are performed to know if the tumor is pituitary or ectopic, such test are.

- CRH stimulation test
- High dose dexamethasone test
- Imaging test
- Petroial sinus sampling test

1.9. Treatment

Treatment is done to maintain the level of cortisol in body and to cure the Cushing's syndrome.

Few ways of treating Cushing's syndrome are as follow[45]

Medical treatment[46]

- Hormone replacement medication may be administered like *ketoconazole*, *mitotane (Lysodren)* and*metyrapone (Metopirone).*
- Mifepristone *(Korlym, Mifeprex)* is approved for people with Cushing syndrome who have type 2 diabetes or glucose intolerance.
- Dopamine-agonist Cabergolineand somatostatine-analogPasireotidecan be administered

Surgical treatment[47]

- In critical condition surgery may be needed to remove a tumor and transsphenoidal surgery.
- Transsphenoidalsurgery cure 70-80% after the operation, 10-years cure 60-70.

Lifestyle changes[48][49]

- Do not suddenly stop consuming glucocorticoids as it may result in life threatening condition called *adrenal crises.*
- One must take enough calcium and vitamin-D in order to cure osteoporosis, regain muscle mass and strength.
- To soothe ache and pain hot bath, massage should to taken and exercise like aerobics should be performed.

2. CONCLUSION

The study was aimed to get information about Cushing's syndrome including its types, causes, signs and symptoms, complications, diagnosis and treatments. In this article we got to know about Cushing's syndrome is caused by prolonged supraphysiological levels of circulating cortisol. Cushing's disease is the most common etiology (70%–80% of Cushing's syndrome cases) of endogenous Cushing's syndrome. It is caused by a pituitary adenoma that secretes adrenocorticotropic hormone (ACTH), which stimulates secretion of cortisol by the adrenal glands. If not effectively treated, Cushing's disease is associated with hypertension, diabetes, obesity, osteoporosis, vascular disease, and shortened life span. Successful resection of a Cushing's disease -associated ACTH-secreting pituitary adenoma results in immediate biochemical remission and preservation of pituitary function. Early identification of Cushing's disease by clinical findings, endocrinological evaluation, and imaging studies is critical for diagnosis and effective surgical management.

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