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A Review on Cushing Syndrome

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Abstract: *"Cushing Syndrome is a hormonal disorder that occurs due to prolonged exposure to high levels of cortisol in the body. This excess cortisol is often the result of abnormal functioning of the adrenal glands or the pituitary gland. Key symptoms of Cushing Syndrome include weight gain, a rounded face, and the presence of purple stretch marks on the skin. Diagnosis typically involves a combination of clinical examinations, blood tests, and imaging studies to identify the underlying cause. Treatment options depend on the cause of the syndrome and may include medications, surgical interventions, or radiation therapy. If left untreated, Cushing Syndrome can lead to serious health complications. This project aims to provide a comprehensive overview of Cushing Syndrome, including its symptoms, diagnostic methods, and treatment options, in order to raise awareness and improve understanding of this condition."*

Keywords: Cushing Syndrome

I. INTRODUCTION

Cushing syndrome is caused by prolonged exposure to high circulating levels of cortisol. The most common cause of cushingoid features is iatrogenic corticosteroid use, while some herbal preparations can also increase circulating corticosteroid levels leading to Cushing syndrome. Cushing syndrome can be interchangeably called hypercortisolism. ACTH-dependent cortisol excess due to a pituitary adenoma is called Cushing disease, and it is responsible for 80% of endogenous Cushing syndrome.[1,2,3]

Cushing's syndrome is a disorder that occurs when your body makes too much of the hormone cortisol over a long period of time. Cortisol is sometimes called the "stress hormone" because it helps your body respond to stress. Cortisol also helps

•Maintain blood pressure
•Regulate blood glucose, also called blood sugar
•Reduce inflammation
•Turn the food you eat into energy

The adrenal glands, two small glands on top of your kidneys, make
Cortisol.[4]

The adrenal glands, two small glands on top of your kidneys, make cortisol. Endogenous Cushing's syndrome is rare. "Endogenous" means something inside your body is causing the disorder rather than

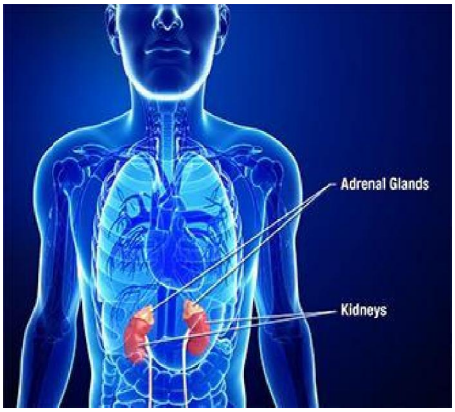

Figure:1

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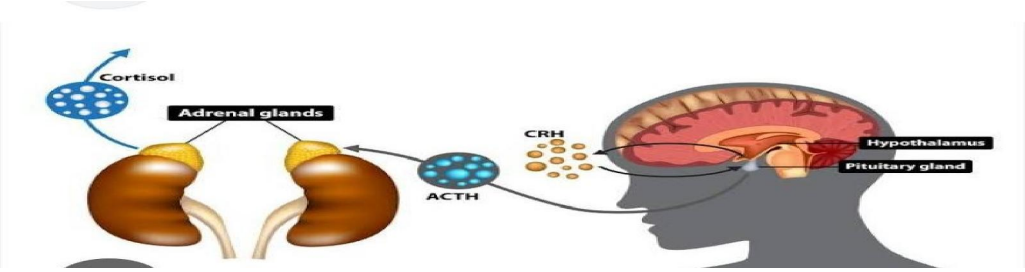
something outside your body, such as medicine. Estimates vary, ranging from about 40 to 70 people out of every million".[5,6]

The pathogenetic mechanisms of endogenous CS can be divided into ACTH-dependent (80% of cases, from a pituitary or other ectopic tumor) and ACTH-independent (20% of cases, due to autonomous adrenal overproduction of cortisol that can depend on either benign or malignant nodules, or by bilateral primary micro- and macronodular adrenocortical hyperplasia).[7]

ACTH-secreting pituitary adenoma is the cause of about 70% of all cases of CS and is termed Cushing's disease (CD). Reported incidence of CD ranges from 1.2 to 2.4 per million people per year in newly diagnosed cases, with a prevalence of 1.2–5.6% of all pituitary tumors. [8]

This can be caused by a tumor of the adrenal glands, the lungs, or the pituitary gland. When the tumor produces too much ACTH, it causes over production of cortisol by the adrenal glands. if the source is the pituitary, it is called Cushing's disease. Cushing's disease occurs more often in women than men and more often occurs between the ages of 20 and 40. [9]



1.2 HISTORY AND PHYSICAL

Patients may have a history of weight gain, fatigue, weakness, delayed wound healing, easy bruising, back pain, bone pain, loss of height, depression, mood swings, emotional reactivity, loss of libido, erectile dysfunction in males, irregular menstrual cycles in females, infertility, hyperhidrosis, hirsutism, biparietal visual loss if there is a large pituitary adenoma, recurrent fungal and bacterial infections due to impaired immunity, and difficulty in combing hair or rising from a sitting position. Psychological problems such as cognitive dysfunction and depression are not uncommon. Some patients may develop severe osteopenia and bone fractures. Patients may also have a history of hypertension, peptic ulcer disease, and diabetes. Physical examination of the patient will reveal increased fat deposits in the upper half of the body leading to "Buffalo torso," characteristic moon facies (earlobes are not visible when viewed from the front), thin arms and legs, acne, hirsutism, proximal muscle weakness of the shoulder and hip girdle muscles, paper-thin skin, abdominal pain due to gut perforation in rare cases, and wide vertical purplish abdominal striae.[10]

Some 70% of people with Cushing syndrome are women or people assigned female at birth (AFAB) and 30% are men or people assigned male at birth (AMAB).

Figure:3

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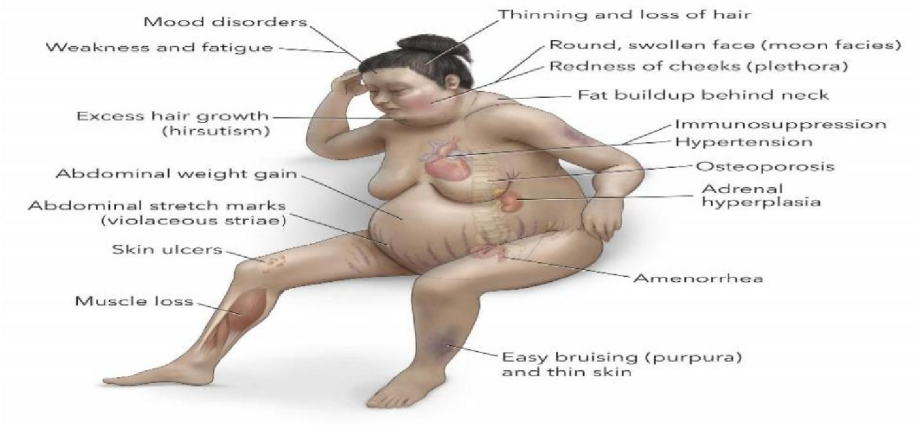

Figure:4

1.2 PATHOPHYSIOLOGY

Cortisol is a steroid hormone produced by the zona fasciculata of the adrenal cortex. After production the cortisol 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%. 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. 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 Kreb's cycle. It promotes the production of free glucose in the body, elevating glucose levels, while simultaneously increasing insulin resistance. 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. It causes detachment of marginating pool of neutrophils in the bloodstream and increases the circulating neutrophil levels although there is no increased production of the neutrophils. This decreased lymphocyte number and increased neutrophils. The corticosteroids mediate the downregulation of NF-kappaB, regulation of AMP kinase, glycogen phosphorylase, 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.[11]

1.3 EPIDERMIOLOGY

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.

However, of the known cases iatrogenic hypercortisolism outweighs the endogenous causes, of the endogenous causes pituitary-mediated ACTH production accounts for 80% of cases of hypercortisolism, followed by adrenals, unknown source, and ectopic ACTH production secondary to malignancies.[12] .

Symptoms

Symptoms of Cushing syndrome can vary depending on the level of extra cortisol.

Common symptoms of Cushing syndrome

- Weight gain in the trunk, with thin arms and legs.
- Weight gain in the face. This is sometimes called moon face.
- A fatty lump between the shoulders. This may be referred to as a buffalo hump.
- Pink or purple stretch marks on the stomach, hips, thighs, breasts and underarms. Thin, frail skin that bruises easily.

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- Slow wound healing.
- Acne

Symptoms women with Cushing syndrome may experience

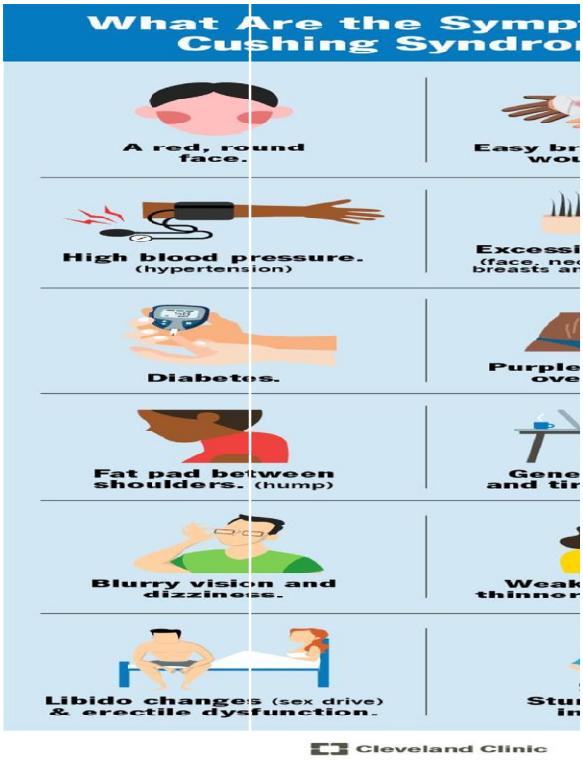
- Thick, dark hair on the face and body. This condition is called hirsutism.
- Periods that are irregular or that stop.[13]

Symptoms men with Cushing syndrome may experience

- Lower sex drive.
- Reduced fertility.
- Problems getting an erection.

Other possible symptoms of Cushing syndrome

- Extreme tiredness.
- Muscle weakness.
- Depression, anxiety and irritability.
- Emotions that are hard to control.
- Trouble concentrating or remembering.
- Sleeplessness.
- High blood pressure.
- Headache.
- Infections.
- Skin darkening.
- Bone loss, which can lead to broken bones. Stunted growth in children.[14]



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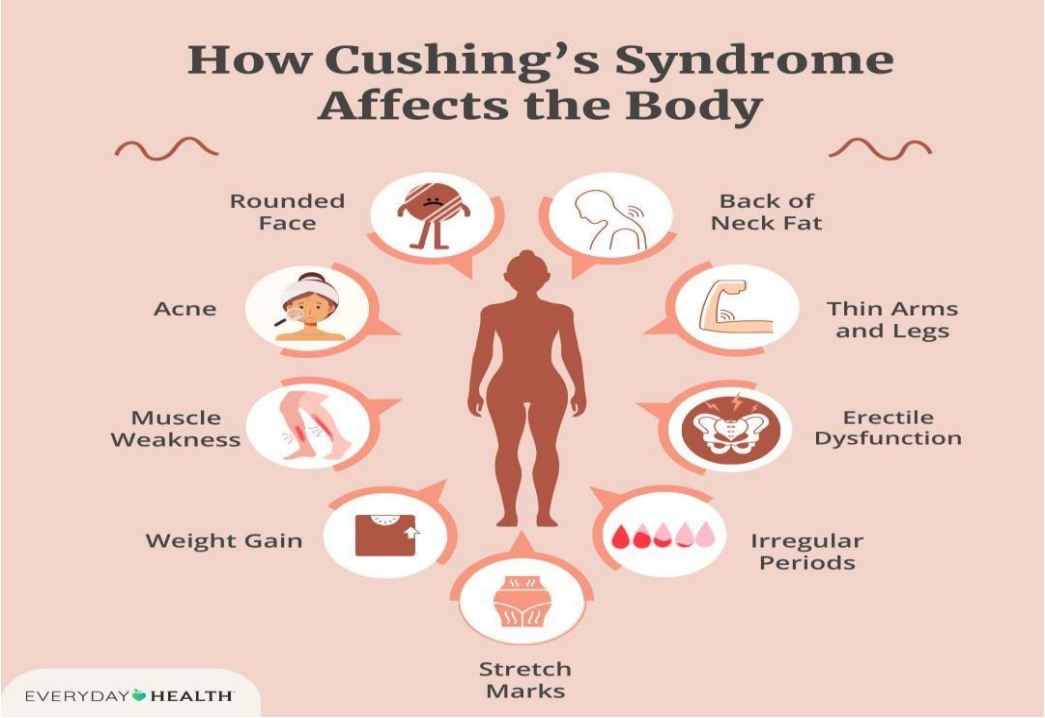

Figure:6

CAUSES

Too much cortisol causes cushing syndrome. There may be many underlying causes of high cortisol level including.

Use of glucocorticoid medication (for example, prednisone) are used to treat many autoimmune disease, such as chronic asthma, rgematoidarthrtis lupus sarcoids and many other disease that result in chronic inflammaton. Chronic treatment with these medication causes "iatrogenic" or exogenous Cushing syndrome. The word "iatrogenic" means that medical treatment has caused something else to happen.[15]

Pituitary tumors Pituitary tumour that make too much ACTH (the hormones that tells the adrenal glands to make cortisole) cause out of 1o cases of cushing syndrome (excluding the cases of atrogeniccushing syndrome) . The name of these type is cushing disease.

Adrenal cortical tumors. A tumor on the adrenal gland ts self can make too much cortisol. these are usually being. However ,the tumor can sometimes be an adrenal cortical carsinoma ,a very rare adrenal cancer.

Lung, pancrease, thyroid and thymus tumors. ectopic ACTH syndrome happens when tumors that develop outside of the pituitary gland produce ACTH. These types of tumors are typically maliganant. The most common type is small cell lung cancer. [16]

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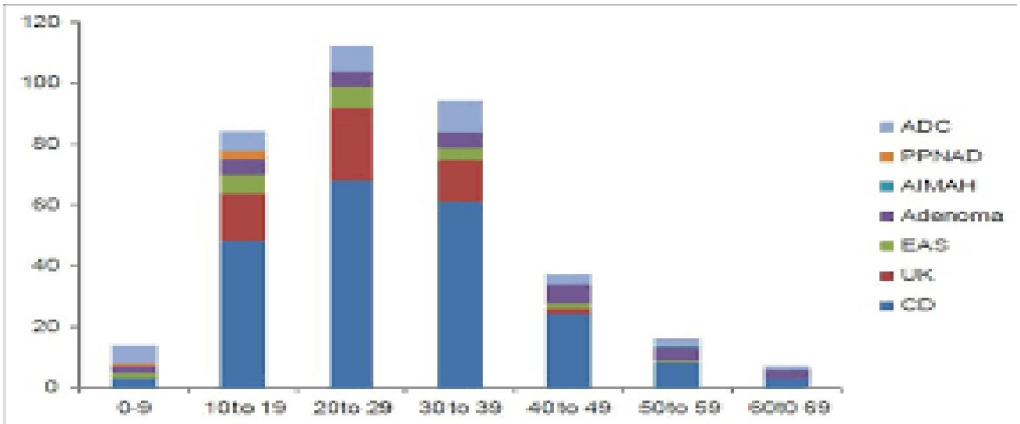

Figure: 7

DIAGNOSIS

The occurrence of any single feature ranges so widely among reported series that no single finding is necessary for diagnosis.[17] Because clinical manifestations depend on both the degree and the duration of hypercortisolism, diagnostic difficulties arise at onset, when signs and symptoms are generally non-specific. However, certain features, such as weakness associated with proximal muscle wasting, skin atrophy, easy bruising after minor trauma, extensive ecchymoses, purple striae produced by the rapid enlargement of trunk and abdomen, hypertension, and psychological changes, strongly suggest hypercortisolism. On the other hand, some patients present with only isolated symptoms. Even the most common findings, such as truncal obesity and hypertension, may be lacking in some cases.[18] The presence of only a few symptoms common to other disorders may be deceptive, and Cushing's syndrome can be misdiagnosed for a long time and patients treated in rheumatological, psychiatric, or other clinics before the correct diagnosis is achieved. Atypical clinical presentations or forms of pseudoCushing's syndrome further complicate the diagnosis. Routine chemistry abnormalities associated with hypercortisolism include neutrophilic leucocytosis, hyperglycaemia, hypokalaemia, hypercholesterolaemia, and hypercoagulable state.[19]

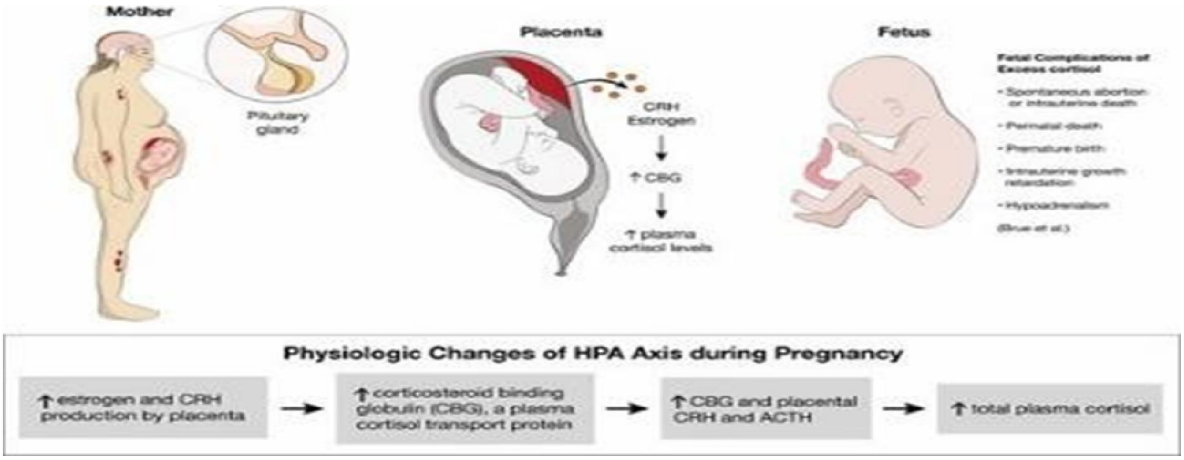

Figure: 8

DIAGNOSIS OF CS IN PREGNANCY:

CS is rarely diagnosed during pregnancy because hypercortisolism inhibits normal follicular development and ovulation. In contrast to non -pregnant patients, the pre-dominant etiology of CS in pregnant patients is adrenal adenomas, found in 40% to 60% of cases.[20] Early diagnosis and management of CS during pregnancy are important

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because of associated fetal and maternal morbidity. Fetal morbidity includes rates of spontaneous abortion, perinatal death, premature birth, and intrauterine growth retardation . Maternal morbidity caused by CS includes hypertension, preeclampsia, wound breakdown, diabetes, fractures, and opportunistic infections. [21]

Clinically, the diagnosis of CS during pregnancy can be more challenging because of overlap in features of hypercortisolism and classic features of pregnancy including fatigue, weight gain, hirsutism, acne, and emotional instability. It has been suggested that when pregnant patients have a triad of hypertension, skin ecchymosis, and muscle atrophy, CS should be considered.[22]

TREATMENT AND MANAGEMENT

The Individualized approach should be followed to evaluate recurrence after surgical resection. Pituitary MRI should be done1-3 months after surgical resection to evaluate success in Cushing disease. Late-night salivary cortisol or serum cortisol or 24-hour urine free cortisol measurement is recommended to ensure eucortisolism after surgical treatment. Radiotherapy is recommended in Cushing disease after failed transsphenoidal surgery or in Cushing disease with mass effect or invasion of surrounding structures.[23] Other oral medications include pasireotide, cabergoline, and mifepristone. In the management of Cushing syndrome, it is crucial to treat comorbidities such as diabetes mellitus, hypertension, osteoporosis, psychiatric issues, and electrolyte disorders. Cushing syndrome due to an ACTH tumor that cannot be resected entirely may require bilateral adrenalectomy followed by lifelong adrenal glucocorticoid replacement (e.g. hydrocortisone) and mineralocorticoid (fludrocortisone).[24]

Treatments for Cushing syndrome are designed to lower the amount of cortisol in the body. The best treatment for you depends on the cause of the syndrome. Options include:

7.1 Reducing glucocorticoid use

If Cushing syndrome is caused by taking glucocorticoid medicine for a long time, your health care provider may be able to control your symptoms by lowering how much medicine you take. This is done carefully over time, while still managing the condition for which you take it. Don't reduce the dose of glucocorticoid drugs or stop taking them on your own. Do so only with help from your health care provider.

Stopping these medicines too quickly can cause you to have too little cortisol in your body. Slowly tapering off the medicine allows your body to make a healthy amount of cortisol. [25]

Surgery

If Cushing syndrome is caused by a tumor, your health care provider may recommend removing the tumor with surgery. Pituitary tumors are often removed by a neurosurgeon, who may do the operation through your nose. ACTH-producing tumors in other parts of the body may be removed with regular surgery or using less-invasive approaches with smaller incisions.

If an ACTH-producing tumor isn't found, or if one can't be fully removed and Cushing syndrome continues, your health care provider may recommend removing the adrenal glands. This is called a bilateral adrenalectomy. This procedure immediately stops the body from making too much cortisol. After both adrenal glands are removed, you may need to take medicines to replace cortisol and another adrenal hormone called aldosterone for the rest of your life.

Adrenal gland tumors can be removed through an incision in the midsection or back. Often, adrenal gland tumors that are noncancerous can be removed with a minimally invasive approach.

After Cushing syndrome surgery, your body won't make enough ACTH. You'll need to take a cortisol replacement medicine to give your body the right amount of cortisol. Most of the time, your body starts making enough cortisol again, and your health care provider can taper off the replacement medicine. Your endocrinologist may use blood tests to help decide if you need cortisol medicine and when it may be stopped.

This process can take from six months to a year or more. Sometimes, people with Cushing syndrome need lifelong replacement medicine. [26]

Radiation therapy

If the surgeon can't totally remove a pituitary tumor, radiation therapy may be needed along with surgery. Radiation also may be used for people who can't have surgery.

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Radiation can be given in small doses over six weeks, or with a single, high dose of radiation. In both cases, your health care provider can plan your procedure in a way that reduces radiation exposure to other tissues.

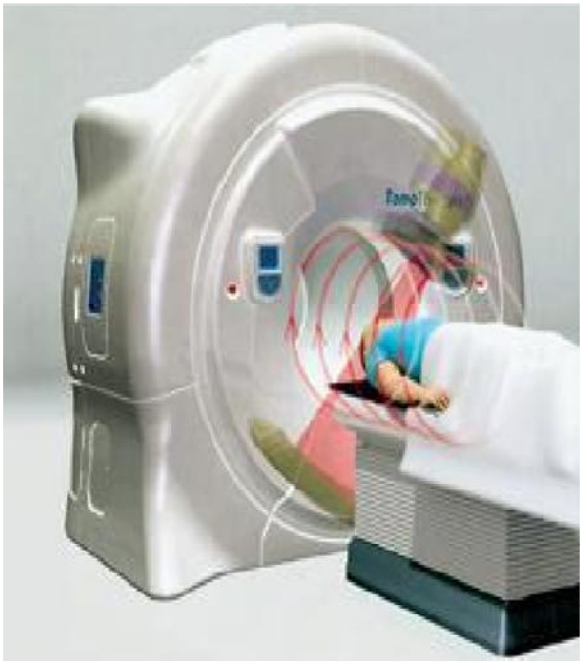

Figure: 9

7.4 Medications

Medicines can be used to control cortisol levels when surgery and radiation don't work or aren't an option. Medicines also might be used before surgery in people who are very sick with Cushing syndrome. This can improve symptoms of the disease and reduce the risks of surgery. Medical therapy for Cushing syndrome is not a cure and may not completely improve all of the symptoms of too much cortisol.

Medicines to control cortisol production at the adrenal gland include ketoconazole, osilodrostat (Isturisa), mitotane (Lysodren), levoketoconazole (Recorlev), and metyrapone (Metopirone).

Mifepristone (Korlym, Mifeprex) is approved for people with Cushing syndrome who have type 2 diabetes or high blood sugar. Mifepristone does not lower the amount of cortisol the body makes, but it blocks the effect of cortisol on tissues.

Pasireotide (Signifor) is given as a shot two times a day. It works by lowering the amount of ACTH from the tumor, which lowers cortisol levels. Other medicines are being developed.[27]

II. CONCLUSION

Cushing syndrome is a rare condition that happens when the body has so much cortisol, a hormone produced by the adrenal glands this can cause a various health problem including weigh gain, high blood pressure, and change in blood.

In simple term the conclusion about cushing syndrome is that it is caused by excess cortisol in the body which can negatively affect a person health in many way. Treatment usually involve addressing the cause of cortisol which can help improve symptoms.

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